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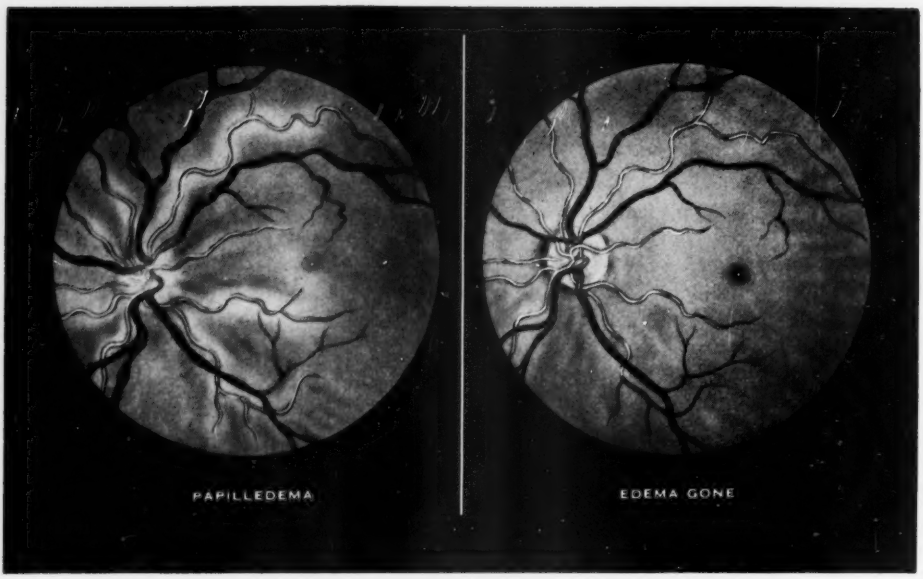

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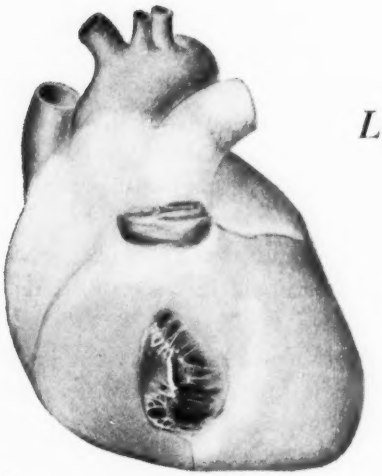

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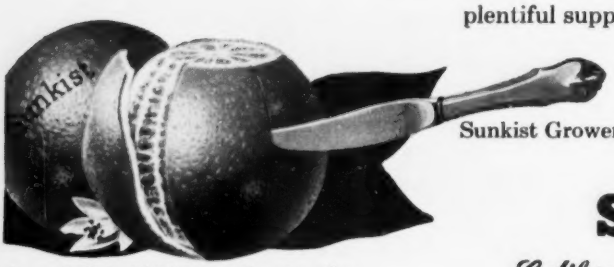

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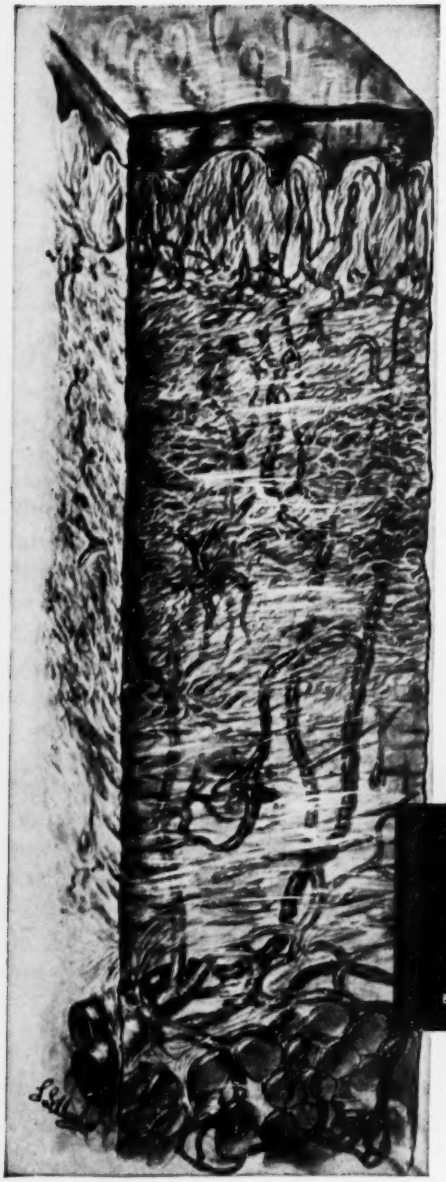

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INSULIN REACTIONS

Manifestations and Need for Recognition of Long-Acting Insulin Reactions

ROBERT K. MADDOCK, M.D.
AND
LEO P. KRALL, M.D.
NORFOLK, VA.

MANY DIABETIC patients have insulin reactions that are undetected even by trained medical personnel. Why such a situation should exist after more than 25 years of intensive experience with insulin poses several questions. Is it because there is less awareness of insulin reactions; have the symptoms changed, or are the symptoms so mild that they are hard to recognize and thus of little or no importance? Perhaps all of these questions may be answered "yes," except that all insulin reactions must be considered to be important. As a result of long experience with regular insulin, sweating, hunger, tremor, and palpitation have become accepted as the principal symptoms of the hypoglycemic state. It has also been long recognized that abnormal behavior, double vision, unconsciousness, and other serious central nervous system symptoms frequently occur if the hypoglycemic state is prolonged or becomes more marked. In fact, judgment of the degree of severity of the insulin reaction was often determined by the severity of the central nervous system symptoms. It has not, however, been generally recognized that headache, minor personality disturbances, difficulty in speech and vision, and automatic behavior, as well as more serious central nervous system symptoms, may occur without any of the generally accepted symptoms of hypoglycemia. Following the introduction and almost universal use of the long-acting insulins, the "central-nervous-system-type" of reaction has become common, and, while the symptoms may be mild, the degree of hypoglycemia may be and often is extreme. In most reactions of this type the intelligence of the patient is reduced to a point at which he cannot be expected to understand the significance of his symptoms. He is thus exposed to the risk of failing to eat or of continuing with physical exertion and thus making the hypoglycemia worse. Should he be driving an automobile, working with dangerous machinery, or even crossing a street, he may be exposed to serious physical danger. The silly behavior or quarrelsomeness displayed by some of these patients has frequently been misinterpreted and has led to accusations of drunkenness or worse. Surely these symptoms are of more than little importance. It is with the better understanding and detection of the "central-nervous-system-type" of insulin reactions caused by long-acting insulins that this paper is principally concerned.

Chief (Dr. Maddock) and Deputy Chief (Dr. Krall), Medical Service, United States Public Health Service Hospital.

MECHANISM OF INSULIN REACTIONS

The mechanism of insulin reactions is poorly understood. Formerly all insulin reactions were considered to be the result of hypoglycemia; however, experience has shown that the severity of the symptoms is not always proportional to the degree of hypoglycemia. In fact, symptoms such as hunger, tremulousness, sweating, and palpitation have frequently been observed in patients with normal or slightly elevated blood sugar.[1] In general these symptoms are mild, but they may be very troublesome to the patient and even prevent good control of his diabetes. Although Joslin [2a] states that no member of his group has observed an insulin reaction associated with a blood sugar level above 80 mg. per 100 cc., he further states that a rapid fall to a level slightly below 100 mg. per 100 cc. might give rise to symptoms that would hardly be felt under normal circumstances. Most observers [3] believe that it is the rapid fall in blood sugar rather than the final level reached that brings about this apparent paradox of hypoglycemic symptoms without hypoglycemia. In sharp contrast with the above is the apparent absence of symptoms in the presence of severe degrees of hypoglycemia. Blood sugar levels as low as 40 to 50 mg. per 100 cc. have frequently been reported [4] in individuals who apparently do not have symptoms. The wording "apparently do not have symptoms" has been used advisedly, since signs of hypoglycemia may often be found after a careful search. While such an individual may not be able to detect symptoms himself and may behave in an apparently normal manner, he should be considered to be normal only to the extent that his behavior at that moment does not seem abnormal. A slight increase in physical or intellectual activity may often quickly reveal the true situation and bring on more obvious symptoms. This type of reaction has become fairly frequent following the use of long-acting insulins and generally occurs following a slow progressive lowering of the blood sugar level. Sleep and the barbiturate drugs are at times responsible for concealing such a hypoglycemic state.

The obvious similarity between such symptoms as sweating, tremulousness, palpitation, etc., produced by an injection of epinephrine and those that occur in hypoglycemia was first pointed out by Boothby and Wilder [5] in 1923. The theory that the symptoms of hypoglycemia might be due to an increase in circulating epinephrine was then further strengthened by the actual demonstration of an increase in circulating vasoconstricting substance, presumably epinephrine, in the

1. John, H. J.: Diabetes: Statistical Study of 1000 Cases, Arch. Int. Med. **39**:67-92 (Jan.) 1927.

2. Joslin, E. P.; Root, H. F.; White, P.; Marble, A., and Bailey, C. C.: The Treatment of Diabetes Mellitus, Ed. 8, Philadelphia, Lea and Febiger, 1946, (*a*) p. 388, (*b*) p. 389.

3. Conn, J. W.: The Diagnosis and Management of Spontaneous Hypoglycemia, J. A. M. A. **134**:130-138 (May 10) 1947. Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1941, p. 11.

4. Barach, J. H.: Diabetes and Its Treatment, New York, Oxford University Press, 1949, p. 294. Duncan, G. G., and others: Diabetes Mellitus: Principles and Treatment, Philadelphia, W. B. Saunders Company, 1951, p. 154. Joslin.[2b]

5. Boothby, W. M., and Wilder, R. M.: Effect of Insulin on Rate of Heat Production and Its Significance in Regard to Calorigenic Action of Adrenalin, M. Clin. North America, **7**:53-56 (July) 1923.

presence of hypoglycemia.[6] It was also shown that epinephrine not only brought about the release of glucose from the glycogen of the liver [7] but also reduced the demands of the peripheral tissues on the circulating glucose.[8] Epinephrine was thus shown to be an effective agent for elevating the blood sugar in the presence of hypoglycemia. This evidence was further supported by the findings of Heilbrunn and Liebert [9] that little or no vasoconstrictor substance was present in the blood of patients going readily into insulin shock whereas those patients who exhibited mild symptoms such as drowsiness and perspiration had an increase in a vasoconstrictor substance, presumably epinephrine.

The association of the symptoms of disturbances in behavior, vision, speech, and consciousness early implicated the central nervous system in the causation of insulin reactions. In 1929 Joslin [10] suggested that the effect of hypoglycemia on the central nervous system might be related to depressed activity of certain oxidative processes similar to that occurring in asphyxia. The demonstration that carbohydrate was the chief or only source of energy for nerve tissue tended to substantiate this theory. Studies by Himwich [11] and others, based on rapidly induced hypoglycemic states in the shock treatment of mental disorders, indicated a correlation between the degree of hypoglycemia and a reduction in activity of various centers of the brain. The higher centers were the first to fail, while a successive failure of lower centers occurred as the blood sugar continued to fall. This theory and the supporting observations are fairly satisfactory in explaining the phenomena observed in hypoglycemic states rapidly induced by shock doses of fast-acting insulin. It does not explain the apparently contradictory nature of the central nervous system's reaction to the more gradually induced hypoglycemia seen in patients receiving long-acting insulins for the treatment of diabetes mellitus. The absence of symptoms in the presence of a blood sugar of 40 mg. per 100 cc. also remains a mystery. In an excellent review of the dynamics of hypoglycemia Fabrykant and Bruger [12] present an interesting theory concerning glycemia and central nervous system activity. It is their belief that too much emphasis has been placed on the fluctuations of the blood sugar level during hypoglycemic reactions and not enough on the dynamics of cerebral sugar metabolism itself. They suggest that the rate of utilization of carbohydrate by the brain must be measured by the rate of cerebral consumption rather than by the rate of supply. Thus, while recognizing the ultimate effect of a low blood sugar, they point out that a decrease in brain sugar and a low blood sugar do not necessarily greatly affect a brain whose carbohydrate requirement is low. They

6. Brandt, F., and Katz, G.: Ztschr. klin. Med. **123**:23, 1933; cited by Fabrykant, M., and Bruger, M.: Dynamics of the Hypoglycemic Reaction, Am. J. Med. Sc. **216**:84-96 (July) 1948.

7. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, Ed. 5, Baltimore, Williams & Wilkins Company, 1950, p. 798.

8. Cori, C. F., and Cori, G. T.: Mechanism of Epinephrine Action: Influence of Epinephrine and Insulin on Carbohydrate Metabolism of Rats in Postabsorptive State, J. Biol. Chem. **79**:321-341 (Sept.) 1928.

9. Heilbrunn, G., and Liebert, E.: Observations on the Adrenalin Level in the Blood Serum During Insulin Hypoglycemia and After Metrazol Convulsions, Endocrinology **25**:354-358 (Sept.) 1939.

10. Joslin, E. P.: The Treatment of Diabetes Mellitus, Ed. 4, Philadelphia, Lea & Febiger, 1928, p. 49.

11. Himwich, H. E.: Hypoglycemic Reactions, Proc. Am. Diabetes A. **2**:159-169, 1942.

12. Fabrykant, M., and Bruger, M.: Dynamics of the Hypoglycemic Reaction, Am. J. Med. Sc. **216**:84-96 (July) 1948.

conclude that the demands of the brain for carbohydrate in the presence of a low blood sugar and the activity of the brain in controlling its own consumption of glucose are of great importance along with the variations in blood glucose in the development of symptoms of hypoglycemia. This concept, if correct, may be used to explain the paradoxical situation of the presence of hypoglycemic symptoms in the absence of hypoglycemia as well as the absence of symptoms in the actual presence of hypoglycemia.

From the foregoing discussion it is obvious that there is no simple explanation for all of the phenomena related to insulin reactions. It is also apparent that the symptoms commonly seen in insulin reactions may be separated into two groups, (1) those probably due to an excess of circulating epinephrine and (2) those due to a depression in function of the central nervous system. While both of these

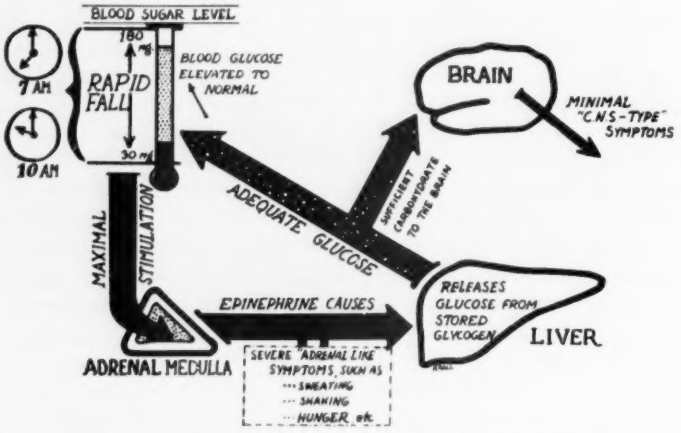

Fig. 1.—Schematic diagram of "adrenalin-like" reactions (usually due to fast-acting insulins).

TABLE 1.—*Symptoms of the "Adrenalin-like" Reaction*

Nervousness	Tachycardia
Tremulousness	Palpitation
Weakness	Sweating
Hunger	Pallor

mechanisms are present in many insulin reactions, the clinical evidence suggests that reactions that are purely of the "adrenalin-like" or "central-nervous-system-type" are frequently seen by themselves.

CLASSIFICATION OF INSULIN REACTIONS

It is suggested that the symptoms commonly seen in insulin reactions be divided into two main types, (1) "adrenalin-like" and (2) "central-nervous-system-type," regardless of whether or not both sets of symptoms may be produced by a single mechanism. This separation of symptoms is not only logical but also permits a clearer visualization of what is occurring in any particular reaction. Even more

important is the increased ability to detect atypical reactions and the better appreciation of the danger of the apparently mild central nervous system reactions that have become so common.

"Adrenalin-like" Reaction.—The symptoms of the "adrenalin-like" reaction are thought to result from an excess of circulating epinephrine (Fig. 1). The entire mechanism by which the adrenal medulla is stimulated to secrete epinephrine following a fall in blood sugar remains unknown. In general, reactions of this type are associated with rapid falls in blood sugar, and for this reason they most commonly follow the injection of fast-acting insulin, sudden and excessive physical activity, or the missing of a meal combined with ordinary physical activity. Occasionally, mild symptoms of this type may be observed in persons with a rapid fall in blood sugar even though a hypoglycemic level is not reached. Since early experience with

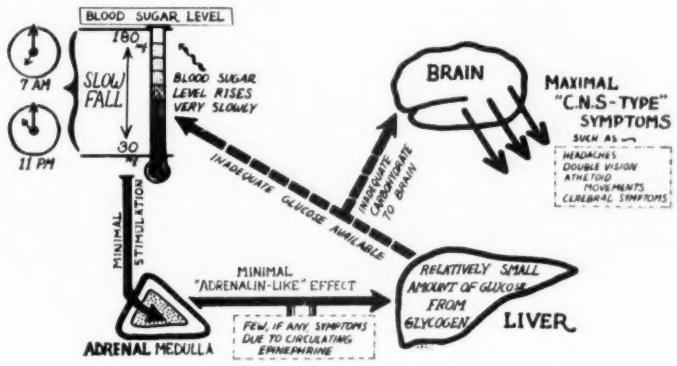

Fig. 2.—Schematic diagram of "central-nervous-system-type" reactions (usually due to slow-acting insulins).

TABLE 2.—*Symptoms of the "Central-Nervous-System-Type" Reaction*

Headache	Crying
Nausea	Automatic behavior
Visual and speech disturbance	Twitching
Slow reactions	Athetoid movements
Mental confusion	Grimacing
Personality changes	Mask-like facies
Laughing and loud talking	Hemiplegia
Anxiety	Convulsions
Depression	Coma

insulin was limited to the fast-acting regular insulin, almost all hypoglycemic states due to insulin reactions were associated with symptoms of the "adrenalin-like" type. For this reason there is little wonder that it was this group of symptoms that became synonymous with the term hypoglycemia, and it is equally not surprising that insulin reactions in which the "adrenalin-like" symptoms are minimal or absent are still overlooked or misinterpreted.

Central-Nervous-System-Type Reactions.—The "central-nervous-system-type" reactions are the result of reduced activity of the central nervous system (Fig. 2). The exact mechanics of this situation remain poorly understood; however, it would

appear that if the nerve cells were deprived of their single source of energy for any considerable period of time serious dysfunction would be bound to result. Should this deprivation continue for a prolonged period, irreparable damage would be expected to occur. Such are the clinical facts. It is also not only possible but probable that during periods of low cerebral activity, as during sleep or relative inactivity, the requirements of the central nervous system for glucose are greatly reduced. For this reason a slowly developing hypoglycemia could remain obscure. Figure 2 graphically portrays a mechanism for the production of the "central-nervous-system-type" of reaction without the presence of the "adrenalin-like" symptoms. The slowly developing hypoglycemia that is produced by the slow-acting insulins does not cause an increase in circulating epinephrine. The absence of the epinephrine explains the absence of the "adrenalin-like" symptoms as well as the failure of the blood sugar to rise and correct the hypoglycemic state. Finally, as a result of a continuing deficiency of blood glucose, there is inadequate cerebral function and the appearance of the "central-nervous-system-type" of insulin reaction.

Mixed Reaction.—Frequently both the "adrenalin-like" and "central-nervous-system-type" symptoms occur in a single reaction, although one or the other generally predominates. A reaction of this type may be visualized as occurring in several ways. In spite of an increase in circulating epinephrine, the blood sugar may fail to rise because of inadequate glycogen stores or an overwhelmingly large amount of insulin. It is also easy to conceive of a slowly developing hypoglycemia with mild central nervous system symptoms which bring on an increase of physical activity, with a consequent rapid drop in the blood sugar. The rapid fall would then stimulate an increase in circulating epinephrine and the development of "adrenalin-like" symptoms.

REPORT OF CASES

CASE 1.—A 37-year-old hook-and-ladder fire engine driver had known diabetes of several years' duration. His diabetes was apparently controlled by 45 units of NPH insulin daily. His physician changed over from the 40-unit to the 80-unit per cubic centimeter type of insulin. The patient apparently did not understand the change and inadvertently doubled his dose. Late each day he suffered from giddiness, acts of irresponsibility, and careless driving. On several days he had convulsive seizures, fortunately while he was off duty. Finally, one day he became unconscious and was brought to the hospital with a tentative diagnosis of "epileptic seizures." Urinalysis on admission showed a 2+ glucose reaction, but the venous blood sugar was 38 mg. per 100 cc. The patient responded rapidly to intravenous injection of 25% dextrose solution. Subsequent reactions were averted by proper instruction of the patient.

Comment.—This case illustrates the potential danger of reactions in people operating automobiles and also the need of careful education of the patient even in the minor details, which though obvious to a physician are often obscure to a patient.

CASE 2.—A 32-year-old male truck driver was treated at home for pneumonia six weeks previous to this hospitalization. Early on the morning of his admission he omitted his breakfast but took his usual dose of 50 units of protamine zinc insulin injection. Later that morning he coughed up some bright red blood. While working at noon he complained of severe chest pain and appeared to be confused. He returned to his office and became cold, appeared to be in shock, and had a seizure described as "clonic convulsions" by a local physician who was called. These convulsions continued for 30 minutes and ceased after the physician gave him a hypodermic injection of morphine sulfate, 15 mg. and atropine sulfate, 0.4 mg. An intravenous injection of phenobarbital, 0.2 gm., was being prepared when the patient became deeply comatose and was sent to the hospital.

On admission to the hospital his respirations were 12 per minute. The immediate impression was "hypoglycemia," and the patient was given an injection of 50 cc. of 50% of dextrose followed by an intravenous drip of 10% dextrose. The first blood specimen, drawn immediately on arrival, was unfortunately dropped in transit to the laboratory. A second specimen, taken after treatment had started, showed a glucose content of 250 mg. per 100 cc. One hour later the patient developed choreiform movements and, although he could follow objects with his eyes, he could not respond to commands. Because of the failure of his central nervous system to respond to energetic therapy with glucose and because of the uncommon manifestations, diagnoses of encephalitis and other central nervous system diseases were considered.

Over a period of one week the patient returned slowly to a normal memory and a state of orientation. It was discovered that he had known diabetes of four years' duration and that he took varying doses of insulin haphazardly and rarely tested his urine sugar.

Complete study revealed active, moderately advanced pulmonary tuberculosis and very brittle diabetes mellitus. When in reaction the patient would be sullen and negativistic, denying any reaction and refusing orange juice. Because of the paucity of "typical" reaction symptoms these manifestations were frequently misinterpreted by trained medical personnel.

As the patient's infectious state subsided, his diabetes was better controlled and the reactions were fewer and milder.

Comment.—This case illustrates many things, including the danger of giving heavy hypnotic or sedative drug doses to semiconscious patients, the train of circumstance or accidents that can help or confuse a diagnosis, and the potentially serious aftermath of a prolonged state of hypoglycemia. Perhaps the most important point is that the patient was probably already in hypoglycemic reaction at the time he refused his breakfast, took his insulin, and went to work. Certainly the protamine zinc insulin taken the morning of his coma had no time to influence the events until much later in the day. It is likely that the peculiar, irrational behavior that causes patients to perform acts which will precipitate a severe reaction are a part of the same hypoglycemic picture.

CASE 3.—This 46-year-old seaman with known diabetes of 10 years' duration had been taking 35 units of protamine zinc insulin daily for eight years without consulting his doctor. At the time of his admission an active, moderately advanced pulmonary tuberculosis was revealed. The patient's diabetes was labile, and he had frequent reactions which were often missed or misinterpreted.

Late in the evening he would become morose and emotional. He complained of the lack of mail from his relatives and entertained paranoid thoughts about his family. No "classic" hypoglycemic symptoms were observed. The patient would not only deny being in reaction but would become manic and argue loudly. His blood sugar varied from 35 to 65 mg. per 100 cc. during several of these episodes. He responded very rapidly to glucose orally or dextrose intravenously, but this had to be administered almost forcibly because of his belligerent attitude.

Comment.—It is frequently necessary for some informed person to interpret a "reaction" in the hospital or home because a patient's judgment may be so warped by hypoglycemia that he cannot be expected to do so himself.

CASE 4.—A 37-year-old female nurse had known diabetes of eight years' duration. The daily dose of insulin was 60 units of protamine zinc insulin.

The patient frequently awakened in the mornings feeling disagreeable and argumentative. Many breakfast-time emotional crises took place with her husband. The patient would refuse to eat and became verbally violent. She would sometimes have dull headaches and an automatic type of behavior. Other times she would be very irritable and unreasonable. Breakfast, when eaten, would transform her into her usual docile, soft-mannered, almost placid self. She responded readily to insulin and diet adjustment.

Comment.—This is a case where the "Taming of the Shrew" was best accomplished by a little judicious breakfast and an adjustment of the insulin dosage.

CASE 5.—A 39-year-old seaman had known diabetes for nine years. He had frequent admissions to the hospital for "neuritis" and insulin reactions of considerable severity. His physician placed him on a regimen of 70 units protamine zinc and 26 units of regular insulin by separate injections each morning. On the day of admission the patient began acting irrationally about 5:00 p.m. He was given two lumps of sugar, which appeared to help him. Two hours later he began to "thrash about" and bit his tongue. He lived some distance in the country, and his brother tried to bring him to the hospital. The patient became violently antagonistic and in the ensuing fracas knocked down his larger and heavier brother. He was admitted to the hospital at 10:00 p.m. in an unconscious state. At this time an emergency test, five hours after the onset of the reaction, showed the blood sugar to be 40 mg. per 100 cc. At no time did the patient have the sweating, shaking, diplopia, headaches, or other of the generally accepted phenomena of hypoglycemia.

Comment.—It was found that this patient had been using 80-unit insulin on the 40-unit side of his insulin syringe. This again shows the need for more effective patient education as well as for the use of standardized syringes, as recommended by the American Diabetes Association.

CASE 6.—A 32-year-old boiler maker with a 15-year diabetic history was admitted to the hospital with a diagnosis of a fractured right hip and diabetic acidosis. The acidosis and the hip fracture were treated, but during the convalescence other patients observed a personality change. Sometimes the patient was very talkative and jolly almost to the point of hysterical laughter at the slightest provocation; other times he became emotional and wept. He had no sweating, shaking, or hunger. It was noted that these signs took place about the same time each evening. Blood sugar was found to be 60 and 65 mg. per 100 cc. on two of these occasions. The patient had been taking 62 units of protamine zinc and 28 units of regular insulin by separate injections each morning. When the protamine zinc dosage was reduced and the patient's supper calories were increased, the symptoms promptly ceased and did not recur.

Comment.—It should be noted that this hypoglycemia was present during the patient's recovery after he started ambulating and the insulin requirement was lessened. His reactions are noteworthy because they were exclusively personality changes.

CASE 7.—A 31-year-old seaman with diabetes of 18 years' duration had numerous hospitalizations for unstable diabetes and suspected Kimmelstiel-Wilson's disease. Control of his diabetes was very erratic, and he had frequent reactions, which sometimes started with a mild diplopia. During these periods of hypoglycemia he would lose his memory and become very emotional. He couldn't cooperate or even cerebrate with any facility. He would become morose and cry readily. His reactions were sometimes so bizarre that the symptoms were not infrequently misinterpreted. In contrast to the other patients, he was always agreeable and willing, but during reactions he was incapable of responding to commands. His progress was steadily downhill, culminating in death. Postmortem examination confirmed the previous impression of intercapillary glomerulosclerosis.

Comment.—It is interesting that most of the reactions of this patient occurred at night and were due to long-acting insulins. His diabetes could best be controlled on multiple doses of the crystalline product. He had some cognizance of this, because he insisted from the very first admission that he could not tolerate "the cloudy insulin."

CASE 8.—A 25-year-old seaman with diabetes of 12 years' known duration was admitted with multiple furunculosis. Prior to admission he had been taking 40 units of protamine zinc insulin each morning. During a prolonged hospital stay he had many complications, including pyelonephritis, serum hepatitis, severe diabetic retinitis, and thrombophlebitis. His insulin doses varied during these complications, and he had many reactions. The patient had lived most of his life in a remote mountain area. He was a silent stolid person, who had little to say at any time.

He posed a problem during his insulin reactions, because in a period of hypoglycemia he would become even more silent and respond with an automatic type of behavior. The staff on duty had to seek him out in order to determine his state of glycemia. In a typical reaction he would sit immobile and almost catatonic, carrying out commands slowly and automatically.

Comment.—This is an example of the long-acting insulin reaction superimposed on a phlegmatic personality. The patient was somewhat whimsical usually. On several occasions peanuts or candy were discovered carefully cached away in the vicinity of his bed. His defense was that if it were not for these concealed sources of glucose he would be in reaction almost all of the time. Because of the difficulty in diagnosing his reactions, this was probably true.

SUMMARY

The mechanism of insulin reactions is discussed, and simple diagrams showing the two most common types, (1) the "adrenalin-like" and (2) "central-nervous-system-type," are presented. This classification is based on the immediate, or trigger, mechanism of the reaction.

The "adrenalin-like" reaction, usually caused by fast-acting crystalline insulin, follows a rapid drop in blood sugar level and a resulting increase in circulating epinephrine. The reaction is characterized by the classic hypoglycemic symptoms of sweating, shaking, hunger, etc., and is easy to detect both by the patient and by trained observers.

The "central-nervous-system type" reaction is usually caused by the slower-acting insulins, such as protamine zinc insulin, and follows slower falls in blood sugar levels. These reaction symptoms are due to impaired central nervous system functions and are characterized by changes in mood, personality, judgment, and behavior as well as by the more mundane signs such as headache and nausea or the more serious central nervous system symptoms culminating in convulsions and coma. This type of reaction is frequently undetected by the patient as well as his associates.

Eight cases exhibiting a variety of "central-nervous-system-type" reaction symptoms are presented. These reactions were generally overlooked by the patient and were at times missed by a previously alerted medical staff. The modern mechanical age poses an increased threat to patients with these reactions because of their frequently impaired judgment, in addition to the threat of serious central nervous system damage unless the hypoglycemia is corrected. [The blood sugar determinations in this series were made with the Folin-Wu technique; it is likely that the true blood sugar levels were even lower.]

Thorough patient instruction is essential, and the patient's associates must be informed of the probable cause of unusual behavior as well as of the value of remedial glucose. It is vitally important to detect mild early alterations in mood, temperament, judgment, or behavior in a patient receiving long-acting insulin, because the patient, even though denying the existence of a reaction, may be in the early stages of a most dangerous type of hypoglycemic reaction.

SYNDROME OF MYELOFIBROSIS

Report of Eight Cases

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THE CONCEPT of myelofibrosis as a disease entity has been controversial for many years. Much debate has centered around its classification and terminology. Diseases which fit the currently recognized syndrome are to be found in the literature under many names. Descriptive terms such as myeloid metaplasia, myelosis, osteosclerosis, agnogenic myeloid metaplasia, pseudoleukemia, hepatosplenomegaly, erythroblastosis, and myelofibrosis have been used to represent the same process.[1] Myelofibrosis generally has been accepted in this institution as the preferable term for this syndrome because of its descriptive proximity to the pathological process.

The object of this paper is to report eight cases we have observed over the last four years and to discuss the clinical and laboratory features that constitute this syndrome.[2] In these cases the clinical diagnosis was confirmed by surgical biopsy of the bone marrow, splenic aspiration, postmortem examination, or combinations of the three procedures.

DEFINITION

The syndrome of myelofibrosis is a fibroproliferative process involving the bone marrow, accompanied by extramedullary hemopoiesis, teardrop poikilocytes, and leucoerythroblastosis. Leucoerythroblastosis is characterized by the presence of immature red and white cells in the peripheral blood.[3]

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2. (*a*) Taylor, H. E., and Simpson, W. W.: Bone Marrow Fibrosis Developing in Aleukemic Myelosis, Blood **5**:348 (April) 1950. (*b*) Footnote 1 *a-d*.

3. Wintrobe, M. M.: Clinical Hematology, Ed. 3, Philadelphia, Lea & Febiger, 1951.

PATHOGENESIS

Cases of myelofibrosis or conditions of related nomenclature have been reported recently in the literature.[4] The controversy about myelofibrosis began over 75 years ago, when Heuck described a case of generalized osteosclerosis, hepatosplenomegaly, and anemia.[5] Since that time the syndrome has been observed in association with and/or has been considered a variant of myelogenous leukemia, a response to toxins, metastatic lesions, infections such as tuberculosis, and the end-stage of polycythemia vera. Frequently a primary form of myelofibrosis occurs, in which precipitating factors are absent. This may result from a physical or functional bone marrow inadequacy resulting in or accompanied by extramedullary hemopoiesis.[6] It is possible that the primary form could occur with other diseases without necessarily being a secondary manifestation. We have observed many instances of metastatic bone lesions not associated with myelofibrosis; however, this may be related to the type of neoplasm. When these two conditions occur together they may be coincidental rather than an instance of metastatic bone lesions producing myelofibrosis as a result of a secondary response. The stimulus for the formation of extramedullary hemopoietic elements in the spleen, liver, lymph nodes, and renal and adrenal tissue is not yet known. It is not considered to represent a neoplasm, leukemia, or a variant of aplastic anemia secondary to known chemical toxins which directly injure the hemopoietic elements.[7]

The leucoerythroblastosis manifested by immature myelocytes and erythrocytes in the peripheral blood is a distinctive laboratory finding.[1d] The extramedullary areas producing hemopoietic elements may release the precursors into the circulation without complete maturation in an attempt to maintain normal peripheral blood levels of erythrocytes, myelocytes, and platelets.

Occasionally cases in which the bone marrow is hyperplastic have been reported.[8] In our series the bone marrows were uniformly hypocellular. This is one of the significant initial findings in myelofibrosis. It is generally agreed that in the advanced stages the marrow becomes hypocellular and fibrotic. Islands of active blood cell formation are frequently found interspersed between fibrotic strands during the progress of the disease. Reticulum cells and bizarre megakaryocytes are scattered occasionally between the fibrous strands or occur in clusters.[9] One might

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8. (*a*) Dameshek, W.: Physiopathology and the Course of Polycythemia Vera as Related to Therapy, J. A. M. A. **142**:790 (March 18) 1950. (*b*) Footnote 1*a*.

9. Footnotes 1*a* and *d* and 2*a*.

aspirate an island of cellular hemopoietic tissue when limiting the bone marrow study to a single sampling, which would produce a misleading impression because the marrow sample was not representative.

The spleen reveals variable hemopoietic activity in the red pulp.[3] The normal architecture is frequently distorted by an increase in the fibroblastic tissue, the bizarre megakaryocytes, and the immature granulocytes and erythrocytes. The splenic follicles are said to take no part in the hemopoietic process.[1a] Interspersed between the follicles are representative forms of erythrocytes, granulocytes, and megakaryocytes in various stages of development. Frequently a semblance of grouping is evident.[1a] The fibrous tissue has been ascribed to a greater deposition of iron in the spleen from increased breakdown of the patient's cells or those supplied by numerous transfusions.[3] The liver is less strikingly involved by the hemopoietic process, but precursors of the three major series are evident in the dilated sinusoids. Varying degrees of blood cell production are occasionally found in the lymph nodes, renal tissue, and adrenal glands.[1a]

REPORT OF CASES

Case 1.—E. S., a 66-year-old white woman, was admitted to the University Hospitals in March, 1947. She complained of headaches, fatigue, and weakness. Physical examination revealed the skin surfaces and abdomen to be normal. Laboratory studies showed the hemoglobin to be 12 gm., the red cell count 4,800,000, and the white cell count 5,900. The differential cell count was 46% segmented polymorphonuclear leucocytes, 3% eosinophiles, 2% basophiles, 45% lymphocytes, and 4% monocytes.

The second admission was in July, 1951, at which time the patient complained of increased fatigue, shortness of breath, and weakness. The liver extended down 5 cm. from the right costal margin, and the spleen was about 5 cm. below the left costal margin. Both organs were smooth, firm, and nontender. Laboratory studies showed the hemoglobin to be 12.5 gm., the red cell count 5,280,000, and the white cell count 21,350. The hematocrit reading was 46%, platelet count 224,000, reticulocyte count 0.8%, bleeding time three minutes, and coagulation time five minutes. The differential cell count was 13.5% band forms, 2% myelocytes, 2.5% metamyelocytes, 0.5% myeloblasts, 4% eosinophiles, 2.0% basophiles, 13.0% lymphocytes, and 1% normoblasts. The peripheral blood smear revealed teardrop poikilocytes and anisocytosis. Bone marrow aspiration from different sites revealed a hypocellular marrow with the cellular elements in normal distribution. Material aspirated from the spleen showed precursors of the myelocytic, erythrocytic, and megakaryocytic series, thus demonstrating the presence of extramedullary hemopoiesis.

The therapy consisted of 300 r of irradiation to the spleen for three days. The white cell count dropped to 12,600, and the spleen appeared to decrease in size.

The patient was last seen by her family physician in September, 1952, at which time he reported her to be weaker and to be losing weight. The red cell count was 3,500,000 and the white cell count was 20,000 at that time.

Case 2.—L. R., a 54-year-old white woman, was first admitted to the University Hospitals in December, 1936. She complained of a painful, tender mass in the left upper quadrant of her abdomen, which had been present for four years. Weakness and fatigue were present. Physical examination revealed a ruddy-faced woman in no acute distress. The liver extended 4 cm. below the right costal margin, and the spleen extended 7 cm. below the left costal margin. Laboratory studies showed the hemoglobin to be 14.3 gm., red cell count 6,500,000, and white cell count 6,000. The peripheral blood smear showed poikilocytosis. The hematocrit reading was 54%, bleeding time three minutes, coagulation time five minutes, reticulocyte count 0.06%, and fragility test normal. The patient was treated with phenylhydrazine on the assumption that she had polycythemia vera. Irradiation was given over the spleen.

The second admission was in October, 1945, at which time the patient complained of increasing fatigue, weakness, and size of the mass in the left upper quadrant of her abdomen. The spleen was enlarged to the brim of the pelvis and the liver extended 5 cm. below the right costal margin. Laboratory studies showed the hemoglobin to be 16 gm., red cell count 6,000,000, and white cell count 6,000. The differential cell count was 13% band forms, 74% segmented polymorphonuclear leucocytes, 4% eosinophiles, 1% basophiles, 7% lymphocytes, 1% monocytes and 16% nucleated red cells. The hematocrit reading was 52%. A peripheral blood smear showed tear-drop poikilocytes and anisocytosis. The treatment consisted of irradiation to the spleen and a phlebotomy, in which 1,000 cc. of blood was removed.

The third admission was in April 1947, at which time the patient's complaints were essentially the same as on previous admission. The liver and spleen had not appreciably changed in size. The laboratory studies showed hemoglobin 14.4 gm., red cell count 6,870,000, and hematocrit reading 54%. The differential cell count was essentially unchanged. It was felt that the poikilocytosis and anisocytosis were unusual for polycythemia vera, but this was continued as the working diagnosis. Therapy consisted of a phlebotomy in which 500 cc. of blood was removed.

The final admission was in January, 1951, at which time distress caused by the enlarged spleen had increased in severity. The spleen and the liver were found to be considerably larger than on previous admissions. The laboratory studies showed the hemoglobin to be 7.5 gm., red cell count 3,260,000, white cell count 5,900, hematocrit reading 28%, and platelet count 48,000. The differential cell count was 1.5% myelocytes, 1.5% metamyelocytes, 0.5% blasts, 17.5% band forms, 46% segmented polymorphonuclear leucocytes, 8.5% eosinophiles, 18.5% lymphocytes and 3.0% nucleated red cells. The peripheral smear showed teardrop poikilocytes and anisocytosis. The platelets appeared unusually large and abnormal in morphology. Bone marrow aspirated from different sites revealed a hypocellular marrow. X-rays of both femurs showed an increased width of the medullary canals, with a decreased amount of cortical bone. These findings were interpreted as being compatible with the clinical diagnosis of myelofibrosis. The patient died suddenly on Jan. 9, 1951.

Postmortem examination revealed a tremendously enlarged spleen, weighing 3,100 gm., and a liver weighing 3,350 gm. Microscopic examination of these organs showed precursors of the erythrocytic, myelocytic and megakaryocytic series, which indicated extramedullary hemopoiesis. Sections of lymph nodes revealed hemopoiesis. The sections of the rib, sternum, and vertebral bone marrow revealed replacement by fibrous tissue.

CASE 3.—W. C., a 68-year-old white man, was first admitted to the University Hospitals in April, 1951. He complained of fullness in his abdomen and difficulty eating solid foods, which had occurred for three months. Physical examination revealed an anemic man in no apparent distress. The spleen and liver did not appear to be enlarged. Laboratory studies showed the hemoglobin to be 11 gm., red cell count 3,200,000, white cell count 5,200, and platelet count 52,000. The differential cell count revealed an occasional blast cell and myelocyte. There were teardrop poikilocytosis and anisocytosis. The platelets were large and bizarre in appearance. Three specimens of bone marrow, aspirated from different sites, showed a hypocellular marrow. A surgical biopsy specimen of the bone marrow was completely fibrotic, with minimal hemopoietic tissue. X-rays of the long bones were normal.

The second admission was in May, 1951, at which time the spleen was found to extend down 3 cm. from the left costal margin and the liver was down 2 cm. Laboratory studies showed the hemoglobin to be 7.4 gm., red cell count 2,620,000, white cell count 4,200, hematocrit reading 27%, platelet count 96,000, and reticulocyte count 3.4%. The differential cell count was 66% segmented polymorphonuclear leucocytes, 2% metamyelocytes, 1% eosinophiles, 1% basophiles, 22% lymphocytes, 6% monocytes, and 2% nucleated red cells. The bleeding time was three minutes, coagulation time six minutes, clot retraction complete, and fragility test normal. The peripheral blood smear showed teardrop poikilocytes and anisocytosis. Splenic aspiration revealed precursors of the erythrocytic, myelocytic, and megakaryocytic series, which indicated the presence of extramedullary hemopoiesis.

Therapy consisted of a 500 cc. transfusion of whole blood, after which the patient signed out of the hospital against medical advice.

CASE 4.—B. C., a 48-year-old white woman, was admitted to the University Hospitals in February, 1950. She complained of weakness, fatigue, and abdominal distress. Physical examination revealed the liver to extend down 6 cm. from the right costal margin, and the spleen 4.5 cm. from the left costal margin. Laboratory studies showed the hemoglobin to be 13.5 gm., red cell count 4,800,000, and white cell count 5,600. The differential cell count was 11% band forms, 20% segmented polymorphonuclear leucocytes, 2% eosinophiles, 8% basophiles, 29% lymphocytes, 5% monocytes, 13% myelocytes, 6% metamyelocytes, 6% blasts, and 4% nucleated red blood cells. The peripheral blood smear revealed teardrop poikilocytes and anisocytosis. There were several large atypical platelets and an occasional small megakaryocyte. Three specimens of bone marrow, aspirated from different sites, showed a hypocellular marrow. A surgical biopsy of the bone marrow revealed the cellular elements largely replaced by fibrous tissue, with an occasional small focus of myeloid and erythroid elements. The x-ray films of the long bones showed a generalized increase in the density of the visualized bones, with mottled areas of radiolucency. There appeared to be thickening of the cortex and narrowing of the marrow space. These findings were interpreted as being compatible with the clinical diagnosis of myelofibrosis. Because of severe abdominal distress, the patient was given 300 r of irradiation to the spleen.

The patient's second admission was in February, 1952, at which time her complaints persisted. The liver and spleen were found to be larger than on previous admission. A small dose, of 300 r, was given to the spleen for three successive days. The white cell count dropped to 2,300, and this therapy had to be discontinued. A recent report from the patient's family physician, in July, 1952, stated that there was further enlargement of the spleen and liver. The red blood cell count at that time was 4,700,000.

CASE 5.—O. S., a 68-year-old white man, was admitted to the University Hospitals in July, 1948. He complained of weight loss, fatigue, weakness, and left upper quadrant abdominal pain and tenderness. Physical examination revealed a chronically ill man. The spleen was enlarged to the level of the iliac crest, and the liver extended down 5 cm. from the right costal margin. There were numerous shotty axillary and inguinal lymph nodes. The skin had several purpuric areas. Laboratory studies showed the hemoglobin to be 13 gm., red cell count 4,900,000, white cell count 45,000, and platelets 142,000. The peripheral blood smear showed numerous myelocytes and nucleated red cells. There was teardrop poikilocytosis and anisocytosis. Bone marrow aspiration showed a hypocellular marrow, with nucleated red cells and myelocytes making up the remaining cellular elements. The diagnosis at that time was myelogenous leukemia. Treatment consisted of irradiation to the spleen, which resulted in a decrease in size and drop in white cell count. The patient was then discharged and subsequently readmitted on several occasions until his last admision on Oct. 25, 1952.

During this interval his symptoms persisted but were transiently relieved by irradiation of the spleen. Numerous specimens of bone marrow, aspirated from different sites, continued to reveal a hypocellular marrow. A surgical biopsy of the bone marrow revealed abundant fibrous tissue, which had largely replaced the marrow elements. White blood cell precursors were more evident than the red cell precursors in the remaining marrow. Material aspirated from the spleen revealed erythrocytic, myelocytic, and megakaryocytic precursors, giving evidence of extramedullary hemopoiesis. With the accumulation of these laboratory findings, the disease was considered to be myelofibrosis rather that myelogenous leukemia. The last course of irradiation of the spleen was in July, 1952, at which time the red blood cell count was normal but the white cell count was still elevated. When the patient was readmitted for the final time, he was depressed and extremely weak and complained of severe left upper abdominal pain. The red cell count was 2,940,000, white count 8,800, and hemoglobin 8.4 gm. On Oct. 25, 1952, the patient accidentally fell out of bed; subsequently coma developed, and he died.

Postmortem examination did not reveal the immediate cause of death. The liver and spleen were greatly enlarged. Microscopic examination revealed extramedullary hemopoiesis in the spleen, liver, and lymph nodes. Abnormal immature megakaryocytes were conspicuous in these organs. Sections of the bone marrow from the rib, sternum, and femur showed a replacement of the marrow elements by fibrous tissue, with few cellular elements remaining.

CASE 6.—E. U., a 46-year-old white man, was admitted to the University Hospitals in November, 1952. He complained of having had weakness, fatigue, and abdominal distress for eight months. During the last two months he had noted a mass in his left upper abdominal

quadrant. Physical examination revealed a pale man who did not appear to be in any distress. The liver was enlarged and extended 5 cm. below the right costal margin. The spleen extended down to the level of the iliac crest and out to the midline of the abdomen. A few shotty axillary nodes were observed. Laboratory studies showed the hemoglobin to be 12.5 gm., red cell count 3,200,000, white cell count 18,000, platelets 166,000, hematocrit reading 39%, and reticulocyte count 5.4%. The differential cell count was 22.5% segmented polymorphonuclear cells, 25.5% band forms, 9.0% metamyelocytes, 3.5% promyelocytes, 1% eosinophiles, 3% basophiles, 0.5% monocytes, 16.5% lymphocytes, and 6.0% nucleated red cells. The peripheral blood smear showed anisocytosis, poikilocytosis, polychromasia, basophilic stippling, and an occasional large abnormal platelet. Two specimens of bone marrow, aspirated from different sites, revealed a hypocellular marrow with a normal distribution of the remaining cells. Teardrop poikilocytes were conspicuous. A surgical biopsy of the bone marrow revealed fibrous tissue largely replacing the marrow elements. Material aspirated from the spleen showed evidence of hemopoiesis occurring in this organ. The patient was given supportive therapy and discharged, to be followed in the outpatient clinic.

CASE 7.—H. K., a 68-year-old white man, was admitted to the University Hospitals on Feb. 26, 1949. He complained of having had fatigability, progressive weight loss, and weakness for six months. Purpuric showers developed over his legs and thighs, associated with abdominal distention which had occurred in the last two months. Physical examination revealed a very pale man with purpuric spots over his thighs and legs. The abdomen was distended and tympanitic. The spleen was enlarged and extended 6 cm. below the left costal margin. The laboratory studies showed the hemoglobin to be 5.5 gm., red cell count 1,960,000, white cell count 8,200, hematocrit reading 17%, bleeding time five minutes, coagulation time six minutes, platelet count 15,000, and reticulocyte count 3.5%. The differential cell count was 13% lymphocytes, 3% monocytes, 15% band forms, 3% eosinophiles, 1% metamyelocytes, 65% segmented polymorphonuclear cells, and 22% nucleated red cells. The peripheral blood smear showed poikilocytosis and anisocytosis. The surgical biopsy of the bone marrow revealed the marrow spaces to be filled with fibrous tissue. Virtually no evidence of hemopoietic tissue was present. Therapy consisted of blood transfusions and 300 r of irradiation over the splenic area. About 12 hours after the irradiation of the spleen, acute left upper quadrant abdominal pain developed. He went into shock rapidly and died on March 1, 1949.

The postmortem examination revealed the immediate cause of death as intra-abdominal hemorrhage secondary to a ruptured spleen. The spleen was enlarged, and the sections showed an increase in fibroblastic tissue. Immature forms of erythrocytic, myelocytic, and megakaryocytic elements were present, indicating hemopoiesis. Sections of the liver showed similar immature forms in the sinusoids, indicating hemopoiesis. Lymph nodes were involved in the extramedullary blood-forming process too. The bone marrow sections from the rib, sternum, and femur showed diffuse fibrosis.

CASE 8.—L. E., a 45-year-old white man, was admitted to the University Hospitals on April 16, 1949. He complained of weakness, cough and weight loss, which had occurred for the last five months. One week prior to admission he had mild hemoptysis. Physical examination revealed a chronically ill man in moderate respiratory distress. The abdomen did not reveal any enlarged solid organs or masses. The laboratory studies showed hemoglobin to be 7.5 gm., red cell count 2,500,000, white cell count 11,000, and hematocrit reading 21%. The bleeding time was 10 minutes, and there was no coagulation at the end of two hours. The differential cell count was 14% band forms, 52% segmented polymorphonuclear cells, 21% lymphocytes, 5% monocytes, 6% eosinophiles, and 11% nucleated red cells. The bone marrow, aspirated from two different sites, was considered hypocellular but unsatisfactory because of what was interpreted as peripheral blood dilution. The Meyers test for occult blood in stool showed a 3+ positive reaction. The gastrointestinal examination showed a filling defect in the stomach, interpreted as carcinoma of the stomach. The patient received several transfusions, but his condition grew steadily worse. He died on April 30, 1949.

The postmortem examination revealed a primary adenocarcinoma of the stomach which had metastasized to the lungs, spleen, liver, and the bone marrow. The spleen and liver were grossly enlarged. Microscopic sections of the bone marrow from the rib, sternum, and femur showed extensive fibrosis replacing the cellular elements. Nests of malignant cells were interspersed

TABLE 1.—*Cases of Myelofibrosis Reviewed at the State University of Iowa*

	L. R.	O. S.	W. C.	B. C.	E. S.	H. K.	E. U.	L. E.	Cases, No.
Age (average, 56 years)	38	68	68	48	66	68	46	45	..
Weakness	+	+	+	+	+	+	+	+	8
Fatigue	+	+	+	+	+	+	+	+	8
Weight loss	+	+	0	0	0	+	0	+	4
Primary, idiopathic myelofibrosis	+	+	+	+	+	+	+	..	7
Secondary myelofibrosis	..	..	..	..	..	..	..	+	1
Large spleen	+	+	+	+	+	+	+	+	8
Large liver	+	+	+	0	+	+	+	+	7
Lymph nodes	0	+	0	0	0	0	+	0	2
Purpura	+	+	0	0	0	+	0	0	3
X-ray changes, long bones	+	0	0	+	N.D.*	N.D.	0	N.D.	2
Fibrotic marrow by biopsy	+	+	+	+	N.D.	+	+	+	7
Extramedullary hemopoiesis	0	+	+	N.D.	+	+	+	+	6
Hypocellular marrow	+	+	+	+	+	+	+	+	8
Anemia, variable degree	0	0	+	0	0	+	+	+	4
White blood cell count	Norm	High	Norm	Norm	High	Norm	High	Norm	5 normal 3 high
Platelet count	Low	Norm	Low	Norm	Norm	N.D.	Low	N.D.	3 low, 3 normal
Leucoerythroblastosis	+	+	+	+	+	+	+	+	8
Teardrop poikilocytes	+	+	+	+	+	+?	+	0	7
Large abnormal platelets	+	+	+	+	0	0	+	0	5
Duration of symptoms (average, 3½ years)	15 yr.	4 yr.	2 yr.	2 yr.	5 yr.	6 mo.	9 mo.	5 mo.	..
Autopsied	+	+	..	..	..	+	..	+	4
Irradiation to spleen	0	+	0	+	+	+	0	0	4

* N.D. = Not Done.

TABLE 2.—*Myelofibrosis and Related Conditions*

Classification	Signs and Symptoms	Laboratory Findings *	Pathology
Myelofibrosis Primary Secondary	Liver and spleen enlarged Weakness Weight loss Purpura Bleeding	RBC variable, but anemia terminally WBC high, low, or normal Peripheral blood, immature RBC and WBC Platelets, high or low Large bizarre platelets and megakaryocyte fragments in peripheral blood Teardrop poikilocytes Bone marrow aspirate reveals hypocellular marrow Splenic aspirate shows extramedullary hematopoiesis Bone marrow biopsy shows fibrosis	Fibrous connective tissue replacement of bone marrow Extramedullary hematopoiesis in spleen, liver, lymph nodes, and renal capsule Splenic architecture distorted, with increased fibrous tissue, precursors of red and white cells, and megakaryocytes Liver sinusoids distended with hemopoietic elements
Chronic myelocytic leukemia Primary Neutrophilic Basophilic Eosinophilic	Liver and spleen enlarged Peripheral lymphadenopathy Bleeding Fever Skin leukemids occasionally	WBC high, occasionally low or normal Peripheral blood, immature white cells predominate Immature red cells uncommon in peripheral blood Anisocytosis and occasionally poikilocytosis Bone marrow aspirate hypercellular, with predominantly immature myeloid elements	Splenic architecture distorted or destroyed by infiltrating immature myeloid cells Megakaryocytes are unusual in spleen Bone marrow is hypercellular, with predominantly immature myelocytic elements Lymph node architecture altered by infiltrating immature myeloid elements
Erythremia (polycythemia vera)	Large spleen in 75% of cases Large liver in 40% of cases Bleeding Ruddy cyanosis	High RBC, Hb, and hematocrit value Poikilocytosis unusual Occasional normoblast in peripheral blood High WBC, with occasional immature white cell in peripheral blood Bone marrow aspirate hypercellular Blood volume increased O_2 saturation normal	Bone marrow is hyperplastic, with normal distribution of marrow elements usually Spleen is enlarged and congested, mature peripheral blood elements

* The abbreviations are as follows: RBC, red blood cells; WBC, white blood cells; Hb, hemoglobin; O_2, oxygen.

between the fibrous connective tissue. Few marrow elements were seen in the sections examined. The liver and spleen had precursors of the erythrocytic, myelocytic, and megakaryocytic series distending the sinusoids and indicating hemopoiesis.

COMMENT

Differentiation of myelofibrosis from chronic myelocytic leukemia and polycythemia vera is of practical importance. The proper recognition of this condition is essential, because the therapeutic regimen used for myelogenous leukemia and polycythemia vera may hasten death in myelofibrosis. We now think of myelofibrosis as a clinical and pathological syndrome, which has reasonably characteristic features that aid in differentiating it from similar processes. This syndrome resembles myelogenous leukemia, in which splenomegaly, hepatomegaly, lymphadenopathy, an occasionally elevated white cell count, and the presence of immature myeloid elements and poikilocytes in the peripheral blood may occur. The bone marrow in myelogenous leukemia, in contradistinction to that found in myelofibrosis, is hypercellular, consisting primarily of myeloid precursors. Surgical biopsy of the bone marrow does not reveal fibroblastic activity replacing the marrow elements as in myelofibrosis. Study of material aspirated from the spleen or of microscopic sections of the spleen in leukemias demonstrates a preponderance of infiltrating myeloid elements rather than a representative distribution of the three major cell family precursors. The presence of the erythrocytic, myelocytic, and megakaryocytic precursors usually indicates hemopoiesis. Emphasis is placed on the abnormalities noted in the peripheral blood smears, which in many of these cases aroused our suspicions and ultimately led us to the diagnosis of myelofibrosis. The peripheral smears in myelofibrosis and myelogenous leukemia are strikingly similar on occasion. Differentiation by this means is difficult, for in both diseases precursors of the myeloid series are present. Nucleated red cells are more frequent in myelofibrosis than in the leukemias. Leucoerythroblastosis was present in all eight cases of this series. Conspicuously prominent in seven cases was the unusual appearance of the erythrocytes, which frequently had a thin tail-like extension and created the appearance of a "teardrop" cell. The presence of these teardrop poikilocytes was not considered diagnostic, but in our experience they have been present in greater numbers in myelofibrosis than in myelogenous leukemia. Anisocytosis occurs in both of these conditions in varying degrees. Large, atypical, pale-staining, agranular platelets were observed in five cases. These forms appear frequently in myelofibrosis and have been thoroughly described by Downy and Carpenter.[10]

Bone marrow was aspirated from several different sites in an attempt to obtain a more comprehensive picture of marrow activity. The smears in our eight cases consistently revealed hypocellularity, with normal distribution of the remaining cellular elements. When there was leucoerythroblastosis and hypocellularity of the marrow, a surgical biopsy of the bone marrow was of definite help in establishing the diagnosis. Such marrow sections were studied in seven cases. Fibrous connective tissue partially or completely replaced the hemopoietic elements in each case. Islands

10. Carpenter, G., and Flory, C. M.: Chronic Non-Leukemic Myelosis, Arch. Int. Med. **67**:489 (March) 1941. Downey, H., and Norland, M.: Hematologic and Histologic Study of a Case of Myeloid Megakaryocytic Hepato-Splenomegaly, Folia haemat. **62**:1, 1939.

of marrow cells were seen occasionally, interspersed between fibrous strands. Splenic aspiration, as described by Morrison, was of aid in confirming the presence of extramedullary hemopoiesis in four cases. The smears of the specimens aspirated from the spleen consistently revealed the presence of megakaryocytes, immature erythrocytes, and myelocytes, indicating the presence of active blood cell formation.[6a]

Dameshek has considered that occasionally the terminal phase of polycythemia vera is manifested by myelofibrosis.[5a] One of our cases (Case 2; patient L. R.) was initially reported as polycythemia vera, but adequate verification by such studies as the blood volume and peripheral oxygen saturation level was lacking. The minimally elevated red cell count, hemoglobin, and hematocrit reading were, in themselves, insufficient evidence for establishing the diagnosis of polycythemia vera. Abnormal poikilocytes were first noted on initial examination, 16 years ago. Gardner considers that poikilocytosis and anisocytosis in the absence of hypochromia do not occur in any state other than myelofibrosis.[11] A relative polycythemia occasionally may be the initial phase of myelofibrosis rather than myelofibrosis being the terminal phase of polycythemia vera.

All our patients were over 38 years of age at the onset of symptoms. Weakness, fatigue, abdominal distress, and weight loss were the most common complaints. We were unable to discover other diseases in seven cases and classified these as primary. In one case there was an associated adenocarcinoma of the stomach with bone marrow involvement. The relationship of this type of tumor to myelofibrosis remains undetermined. Splenomegaly occurred in eight cases. The spleen varied in size from being just palpable to extension below the iliac crest. Hepatomegaly occurred in seven cases but was less striking. Variable degrees of lymphadenopathy were present in two cases. X-ray films of the long bones demonstrated variable changes in two cases of the five studied. Initially the red cell count was low in four cases, normal in three, and elevated to polycythemic levels in one. The white cell counts ranged from high to low, and this result was not helpful in diagnosis. The platelet count was low in three cases.

Postmortem examinations were performed in four cases. Splenomegaly, hepatomegaly, and lymphadenopathy were consistent findings. Sections of the spleen, liver, and lymph nodes revealed erythrocytic and myelocytic precursors accompanied by megakaryocytes, which distorted the normal or somewhat fibrotic structure of these organs. The presence of precursors from the three major families was considered evidence of active blood cell formation. Sections of bone marrow from the rib, sternum, and femur showed replacement of marrow elements by fibrous tissue. Occasional islands of marrow elements were interspersed between the fibrous strands. Neoplastic cells were scattered about the fibrotic sections in Case 8.

THERAPY

Previous reports in the literature suggest that splenectomy or splenic irradiation are contraindicated in myelofibrosis because of the hemopoietic function of the spleen.[4c] In four cases splenic irradiation was resorted to in an attempt to relieve the abdominal distress caused by the enlarged spleen. Irradiation reduced the size

11. Gardner, F. H.: Clinical Pathological Conference, New England J. Med. **246**:623 (April 17) 1952.

of this organ temporarily and produced some relief of the severe abdominal distress. Red cell counts did not drop precipitously in any patient we treated, but we felt that it contributed to the earlier onset of terminal anemia in patient O. S. (Case 5). This procedure is not without direct hazard. H. K. (Case 7) died of intraperitoneal hemorrhage as a result of splenic rupture which occurred 12 hours after he received only 300 r of irradiation to the spleen. Possibly the small amount of swelling and edema produced by irradiation was sufficient in this case to rupture the capsule.

Recent reports in which radioactive iron was used to demonstrate the rate of hemopoiesis in patients with myelofibrosis following irradiation to the spleen revealed a decreased production of red cells, an increased severity of anemia, and a precipitously rapid terminal course.[12]

SUMMARY

The syndrome of myelofibrosis is still poorly understood. There is still debate about terminology, classification, and etiology. Clinically and pathologically this syndrome is a fibroproliferative process diffusely involving the bone marrow and accompanied by extramedullary hemopoiesis, teardrop poikilocytes, and leucoerythroblastosis. Hypocellular bone marrow, leucoerythroblastosis, and splenomegaly were consistently found in our cases. Teardrop poikilocytes were evident in six cases, and their presence was one of the initial laboratory findings that helped in the eventual diagnosis. Fibrotic bone marrow sections were demonstrated in seven cases, and the presence of extramedullary hemopoiesis in the spleen was established in six cases. Large pale-staining atypical platelets were found in five cases.

Differentiation of myelofibrosis from myelogenous leukemia and polycythemia vera is of practical therapeutic importance. The similarity of these diseases is striking at times, but the combination of fibrosis of the bone marrow, extramedullary hemopoiesis, leucoerythroblastosis and teardrop poikilocytes occurs principally in myelofibrosis. Irradiation therapy to the spleen has been used frequently in the past, either to relieve the abdominal distress created by the enlarged spleen or as a therapeutic procedure when the findings were interpreted as representing leukemia or polycythemia. In the light of our present knowledge and experience we believe that this therapy in myelofibrosis should be reserved for patients in whom abdominal pain is incapacitating and then used only when there is other evidence of extramedullary hemopoiesis. Supportive therapy with transfusions to maintain the red cell count is the only help at this time.

CONCLUSIONS

1. The syndrome of myelofibrosis is a fibroproliferative process diffusely involving the bone marrow and accompanied by extramedullary hemopoiesis, leucoerythroblastosis, and teardrop poikilocytes.

2. The syndrome of myelofibrosis may be strikingly similar to that of myelogenous leukemia or polycythemia vera and should be differentiated from these diseases.

12. Wasserman, L. R.; Rashkoff, I. A.; Leavitt, D.; Mayer, J., and Port, S.: The Rate of Removal of Radioactive Iron from Plasma: An Index of Erythropoiesis, J. Clin. Invest. **31**:32 (Jan.) 1952.

3. Bone marrow aspirations from different sites are needed to obtain a more comprehensive picture of over-all marrow activity.

4. Surgical biopsies of the bone marrow help confirm the presence of a fibroproliferative process.

5. Material aspirated from the spleen demonstrates the presence of hemopoiesis in this organ.

6. The presence of teardrop poikilocytes was one of the initial findings that was present in most of our cases.

7. Therapy in myelofibrosis is generally supportive. Irradiation to the spleen is not without hazard and should be used only to relieve incapacitating abdominal pain when other areas of extramedullary hemopoiesis are evident.

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CLINICAL METHOD FOR MEASURING CAPILLARY BLOOD PRESSURE AND ITS APPLICATION IN HYPERTENSION

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A PRACTICAL reliable method for the measurement of capillary pressure in man could prove to be an important tool in the elucidation of certain problems of disease as well as in facilitating physiological and pharmacological studies. Methods have been available for the determination of capillary pressure in man, but in their present form they are unsatisfactory. Danzer and Hooker,[1] in 1920, described their method, in which nailbed capillaries were observed microscopically, the blood flow within them was watched, the flow obliterated by applying direct external pressure, and the pressure gradually reduced until normal capillary flow reappeared. The pressure at which this occurred was taken as a measure of capillary pressure. Several modifications of this method have been introduced, but none has come into general use because the apparatus and technique used in applying direct external pressure are unsuitable for clinical observations. A review of the various methods (and a new method) will be found in the comprehensive paper by Strax and DeGraff [2] (1931). Landis,[3] in 1930, described direct determination of capillary pressures by introducing a micropipette into the lumen of the capillary. His figures are the standard for capillary pressure. This remarkable method is unsuitable for clinical work. The technique proves arduous for patient and physician. Eichna and Bordley [4] (1939) have compared the direct and indirect methods of taking capillary pressures. They concluded that the indirect methods are unreliable, but the difficulties of the Landis method were not minimized. In the present paper a clinical method for the determination of capillary pressure is described.

METHOD

Over more than 10 years I have made several thousand systematic observations on the nailbed in health and disease by capillary microscopy. In order to estimate capillary pressure the principle of ordinary clinical sphygmomanometry was adapted for the nailbed. A manometer cuff made for the newborn infant's arm was attached to an ordinary sphygmomanometer and fastened around the second phalanx and distal interphalangeal joint of the finger. The nailbed capillaries were observed under the microscope (Davis,[5] 1945, 1946). The pressure in the cuff was quickly elevated until all visible capillary blood flow stopped. The pressure was then reduced until normal flow reappeared in several capillaries. This pressure was taken as a measurement of capillary pressure. (This procedure must surely have been done before, yet I have not seen it reported.)

From the Rothschild-Hadassah-University Hospital.

1. Danzer, C. S., and Hooker, D. R.: Am. J. Physiol. **52**:136, 1920.
2. Strax, P., and DeGraff, A. C.: Am. Heart J. **6**:807, 1931.
3. Landis, E. M.: Heart **15**:209, 1930.
4. Eichna, L. W., and Bordley, J., III: J. Clin. Invest. **18**:695, 1939.
5. Davis, E.: Proc. Roy. Soc. Med. **39**:314, 1945; Am. J. M. S. **212**:192, 1946.

Details.—The hand is held at heart level (level of angle of Louis). The pressure in the cuff is quickly elevated. When all visible capillary blood flow has stopped, the pressure is reduced gradually, when the phenomena described by Danzer and Hooker are seen. Three stages may precede normal flow on continued lowering of cuff pressure, (*a*) reversed flow (from venous limb to arterial limb of capillary) may first be seen; (*b*) the red cells may then be seen to oscillate forward and backward in the capillary without making any progress, and (*c*) a very slow forward progress takes place, to be followed by (*d*) normal brisk flow. Any or all of stages *a*, *b*, and *c* may be absent. Normal forward flow may appear in one capillary before the others or in groups of capillaries at different pressures. A few examples of readings will make this clear. Pressures are in millimeters of mercury.

Patient A Pressure 18	First capillary: normal flow at	24
	Second capillary: normal flow at	22
	Most capillaries: normal flow at	18
Patient B Pressure 14	Several capillaries: normal flow at	18
	Most capillaries: normal flow at	14
Patient C Pressure 30	One capillary: normal flow at	40
	Several capillaries: normal flow at	30
	Flow in remaining capillaries not seen	

In patients with normal blood pressure the cuff pressure is quickly raised to 60 and if all flow has stopped the pressure is reduced by five every 30 to 60 seconds. In patients with high blood pressure the cuff pressure is quickly raised to 75 and reduced as before. The pressure is quickly raised, and time is not spent observing slowed flow, oscillation, and reversed flow (which can be seen when the pressure is gradually raised), because prolonging the phase of venous congestion may influence the readings (see below). All readings are taken at least twice and usually three times in the same group of capillaries, and the behaviour of adjacent capillaries is noted. Repeated results are usually consistent.

This simple method reproduces the phenomena described by Danzer and Hooker, and the results are close to those obtained by Landis.

Comment on Method.—(*a*) The visibility of blood flow in capillaries as seen by capillary microscopy varies enormously not only from person to person and from time to time but in the same patient in different nailbeds and even in the same nailbed at any one time. There are patients and times when blood flow is seen in only 2 or 3 capillaries out of a whole field of say 16 to 20 capillaries. Does the reading for these capillaries hold for most of the capillaries in the nailbed? In general it would seem so. Repeating the readings on the same or different capillaries and at different times usually gives similar results.

(*b*) Spontaneous variations in capillary flow are common. Blood flow will begin or cease abruptly when capillaries are observed for even brief periods. These natural variations could conceivably occur while the cuff is on the finger and the pressure raised. The true readings would then be obscured. This possibility emphasizes the need for repeated readings.

(*c*) In a few patients capillary visibility is too poor to see blood flow clearly and pressures cannot be recorded by this method. In other patients blood flow may not be seen at the first examination. Repeated examinations usually yield success.

(*d*) It is conceivable that the very process of taking the pressure may modify the pressure (see below).

(*e*) Readings at the nailbed may not hold for capillaries elsewhere.

(*f*) What are we really measuring? Are we really measuring arteriolar pressure at the periphery rather than capillary pressure?

This last point, like some of those above, would be of no clinical importance if the results obtained by this method were reasonably constant, reproducible, and consistent. Results emerge which show that the method is useful and reliable.

RESULTS

Observations are reported on 130 persons comprising (*a*) a group of 73 with normal blood pressure and (*b*) a group of 57 with high blood pressure.

Capillary Pressure in Persons with Normal Blood Pressure (Table 1, Column 1.)—The 73 examined comprised 4 healthy persons, 17 with chronic rheumatic valvular disease in various stages, and 52 with afebrile mixed medical outpatient conditions. The range of pressure observed was 8 to 74 mm. of mercury, but most persons (43 out of 69) fell into the range 8 to 24, with an average reading of approximately 20 mm. In 8 patients out of 69 the pressure was 45 or higher, and these are discussed later. There was no correlation between age and capillary pressure. Danzer and Hooker's figures were 20 to 24, while Landis' were as follows: for arteriolar limb of capillary, range 21 to 48, average 32; for summit of loop of capillary, range 15 to 32, average 20; for venous limb of capillary, range 6 to 18, average 12. In the indirect method, the pressure gradient within the capillary is not measured.

TABLE 1.—*Analysis of Capillary Pressures*

Capillary Pressure	1. 69 Patients with Normal Blood Pressure,* No.	2. 57 Patients with High Blood Pressure No.
5- 9	5	0
10-14	15	2
15-19	13	8
20-24	15	9
25-29	5	3
30-34	4	6
35-39	1	2
40-44	3	4
45-74	8†	23‡

* Four healthy persons had pressures of 18, 22, 18, and 20, respectively.
† See Table 2.
‡ See Table 3.

It may well be that just as there is a wide range of normal systolic and diastolic pressures so there is a wide physiological range of capillary pressure. In this paper, patients are considered in two groups: those with higher capillary pressures, and those with pressures in the "normal" range. Analysis of the complete results indicates that pressures of 45 or more may reasonably be considered high.

Capillary Pressure in Hypertension.—Capillary pressures were determined in 57 patients with hypertension (Table 1, Column 2 and Table 2). There emerged a group of 23 patients in whom the capillary pressure was 45 mm. or more and a group of 34 patients in whom the capillary pressure was less than 45. Of the 23 with the higher capillary pressures, all had diastolic pressures of 95 or more. Of the 34 with normal capillary pressures, 28 had diastolic pressures of 95 or more and 6 had diastolic pressures of less than 95. High capillary pressure is not a direct consequence of high diastolic pressure. There was no correlation between the absolute height of diastolic pressure and capillary pressure once the diastolic pressure had reached 95. Very high diastolic pressures do not necessarily mean high or very high capillary pressures.

From Table 1 (Column 2) it will be seen that in hypertension, even when capillary pressures are less than 45, the average capillary pressure is greater than in normal blood pressure. Of 5 patients, with essential hypertension without symptoms or complications among the group of 57, none showed high capillary pressure. This observation must be checked on a larger series. Mufson [6] (1932), using the Danzer and Hooker method, found the capillary pressure to be near the upper limit of normal in essential hypertension.

The hypertensive patients with high capillary pressures had the same age distribution as those with normal capillary pressures. The high capillary pressures were found particularly in patients clinically ill.

The capillary morphology at the nailbed was studied in all patients, using the criteria of Davis and Lee [7] (1953). Of 34 hypertensive patients with normal capillary pressure, 13 had normal capillary morphology and 21 had pathological capillaries. Of the 23 with high capillary pressure, 4 had normal capillary morphology and 19 had abnormal capillaries.

TABLE 2.—*Analysis of High Capillary Pressure (23 Patients) in the Group of Those with High Blood Pressure*

Capillary Pressure	Patients, No.	Patients with Albuminuria, No.
45-49	7	2
50-54	7	1
55-59	2	2
60-64	2	0
65-69	2	1
70-74	3	3

Of the 57 hypertensive patients, 13 had albuminuria and 9 of the latter had high capillary pressures with pathological capillary morphology. Severe chronic renal damage was strikingly associated with high capillary pressure and marked capillary morphological changes. Mufson reported that some of his patients with chronic nephritis had high capillary pressure.

Hypertensive patients with fundus changes I or II (Keith, Wagener, and Barker,[8] 1939) had normal or high capillary pressures in similar percentages, but five showing fundus changes III or IV all had high capillary pressures.

As regards cardiac complications, in my series there was no significant difference between hypertensive patients with normal capillary pressure and those with high capillary pressure. In each group there were two patients with severe coronary insufficiency. In the former group three others had significant cardiac pathology, and in the latter group there were two others.

As regards cerebral vascular disturbances, none occurred in hypertensive patients with normal capillary pressure, but in those with high capillary pressure three had persistent hemiplegia and two others had transitory paralyses. This observation must also be checked in a larger series.

6. Mufson, I.: Am. J. M. Sc. **183**:632, 1932.

7. Davis, E., and Lee, R. E., to be published.

8. Keith, N. M.; Wagener, H. P., and Barker, N. W.: Am. J. M. Sc. **197**:332, 1939.

Patients with Normal Blood Pressure and High Capillary Pressure (Table 3).—Of 69 with normal blood pressure, 8 had a capillary pressure of 45 or more. In the patient with atheroma and in the one with nephritis the results are not surprising. Atheroma without hypertension can be associated with the same complications as occur when hypertension is present. High capillary pressure may turn out to be an important factor in the production of purpura simplex, but it is premature to theorize about these and the remaining cases. But, while it is likely that high capillary pressure would be specially associated with high diastolic pressures of 95 mm. or more, it would be surprising if high capillary pressures were not sometimes found in persons with normal blood pressure. It is likely that a number of factors could raise local capillary pressure without producing a general rise in blood pressure.

Increasing Capillary Pressure on Repeated Measurements of Pressure.—Of 130 patients in whom capillary pressures were measured, 14 showed clearly the phenomenon of a steep rise in capillary pressure as the readings were repeated. Here are some examples:

TABLE 3.—*Patients with Normal Blood Pressure Who Had High Capillary Pressure (Eight Patients)*

Capillary Pressure	Patients, No.	Diseases*
45-49	2	Atheroma (1) Purpura simplex (1)
50-54	4	Purpura simplex (2) Rheumatic valvulitis (1) Peripheral vasomotor disturbance (1)
55-69	0	.....
70-74	2	Disseminated lupus erythematosus (1) Chronic nephritis (1)

* The number of patients who had each disease is given in parentheses.

Healthy man, age 35: first reading 15, second 20, third 25.

Girl, age 13, with migraine: first 4 readings 18, fifth and sixth 35, seventh 20.

Man, age 55, with chronic nephritis: first reading 45, second 65, third 70.

Woman, age 66, with essential hypertension, blood pressure 220/110; first reading 50, second 70, third 90, fourth 60.

This phenomenon was seen in 1 of 4 healthy persons; in 3 of 61 patients with miscellaneous conditions, all of whom had normal blood pressure and capillary pressure, in 3 of 8 patients with normal blood pressure and high capillary pressure, in 2 of 34 who had high blood pressure with normal capillary pressure, and in 5 of 23 who had high blood pressure and high capillary pressure. Certain persons have nailbed capillaries sensitive to a high external pressure and react by maintaining capillary flow at much higher pressure than normal. This phenomenon may be related to the observation of Stanton and his associates [9] (1949) that accelerated deep venous blood flow resulted when a sphygmomanometer cuff pressure of 10 to 15 mm. was applied to the outside of the leg.

COMMENT

Comparing this method with the Landis method it will be noted (*a*) that the Landis method gives the gradient of pressure within the capillary; however, in my

9. Stanton, J. R.; Freis, E. D., and Wilkins, R. W.: J. Clin. Invest. **28**:553, 1949.

method it is possible that the pressure at which red-cell oscillation without progression takes place really represents the pressure in the arteriolar limb of the capillary; (*b*) that the pressure reading in the Landis method is precise; in my method the end-point though often sharp is not always so, and there is room for discussion as to which stage of flow represents the true end-point—beginning of flow (even though slow) or normal flow, and (*c*) that in my method it is not known how much external pressure is taken up by overlying tissue before being transmitted to the capillary.

The disadvantages of the Landis method underline the advantages of the suggested method. The Landis method is technically difficult and arduous for patient and physician. Few capillaries can be studied in the course of any one experiment. Because of the great variability of readings in a single capillary, it is practically impossible to get a statistically significant number of readings for a given patient at any one time. On the other hand, the results in both methods may be modified by the nearness of arteriovenous anastomoses, which by opening and closing may disturb pressures in the nearby nailbed capillaries (McLennan, McLennan, and Landis,[10] 1942).

But despite all the objections, results by my relatively simple method are reproducible and consistent. A range of normal capillary pressures is mapped out. In those with high blood pressure, 23 of the 57 patients showed high capillary pressure —in particular those who were clinically ill and those with severe retinal changes, severe renal changes, cerebral involvement, and marked changes in capillary morphology. Cardiac complications, however, were not correlated with high capillary pressures (but it must be stressed that the numbers considered are small). There was no correlation between age and capillary pressure. High capillary pressure is probably an important adverse prognostic sign in high blood pressure.

In some patients, particularly after repeated capillary pressure estimations, there were one or two capillaries in the microscopic field in which blood flow still continued despite a cuff pressure of 70, sometimes 90, or (on two occasions) 120 mm. (this phenomenon rarely lasted more than several minutes). In some capillaries, therefore, flow can continue temporarily despite high obstructive pressures. This mechanism may have physiological importance.

It is tempting to theorize that high capillary pressure is a compensatory mechanism. It may be present to counteract the slower flow seen in certain of these patients or to aid permeability in narrowed vessels with diminished surface area.

SUMMARY

A practical clinical method for measuring capillary pressure by capillary microscopy, based on the principle of sphygmomanometry, is described.

Capillary pressures of 45 mm. of mercury or above are considered high.

Of 57 patients with high blood pressure, 23 had high capillary pressure.

High capillary pressure in patients with high blood pressure was especially asociated with capillaries of pathological morphology and with severe illness, severe retinal changes, severe renal changes, and cerebral complications.

Dr. Ephraim Shorr, Dr. Louis Leiter, and Dr. E. Landis gave assistance and criticism in this work.

10. McLennan, C. E.; McLennan, M. T., and Landis, E. M.: J. Clin. Invest. **21**:319, 1942.

TOLERANCE TO NASOGASTRIC TUBE FEEDINGS

A Comparative Clinical Study of Two Dietary Formulas

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THE PRESENT study was undertaken because of the frequent occurrence of diarrhea among patients receiving a standard tube-feeding formula which has been in use at the Mayo Clinic for five years.[1] While many patients have tolerated the formula well over long periods of time, the incidence of frank diarrhea, sometimes within a few hours of the first feeding, has seemed high enough to cast suspicion on the formula itself as being the causative factor in some instances. An examination of the composition of this formula (Table 1, Tube-Feeding Formula 1) reveals it to be very high in protein and carbohydrate and very low in fat, as compared with a normal diet,[2] with most of the protein and carbohydrate being derived from milk.

The aims of the study were (1) to determine the frequency of occurrence of symptoms of intolerance (particularly diarrhea) among patients taking the standard tube-feeding formula, (2) to determine whether these symptoms were due to peculiarities in composition of the standard formula or whether certain patients would react similarly to any other nutritious mixture when it was administered in the same amount and manner, and (3) to develop a formula for tube feeding which would not cause diarrhea but which would be nutritionally adequate in all food essentials according to the standards set up by the Food and Nutrition Board of the National Research Council.[3]

REVIEW OF THE LITERATURE

A survey of the literature regarding tube feeding in general revealed very little beyond that contained in texts on diet therapy. It would seem that a controlled study of tube-feeding formulas has not been reported.

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1. Mayo Clinic Diet Manual, Committee on Dietetics, Mayo Clinic, Philadelphia, W. B. Saunders Company, 1949, p. 19.

2. The recommended dietary allowances (revised in 1948) of the Food and Nutrition Board, National Research Council, set forth an intake of 2,400 calories, with at least 20 to 25% of these as fat, and 70 gm. of protein for a sedentary man weighing 70 kg.

3. Recommended Dietary Allowances, National Research Council, Food and Nutrition Board, Washington, D. C., Revised Ed., 1948.

Various authors have contributed facts concerning the indications for tube feeding and the manner in which the feeding is best administered.[4] Regarding the latter, the now generally used intragastric continuous drip method is regarded as being distinctly more effective in avoiding distention and regurgitation than the older practice of pouring the feeding through a funnel and thereafter removing the tube, this procedure being repeated three to four times in 24 hours. A search of the literature for information about the composition of the formulas to be used yielded many different formulas which have been recommended by nutritionists, dietotherapists, and physicians [5] but not much evidence concerning their relative merits or

TABLE 1.—*Composition of Formulas for Tube Feeding*

	Amount, Gm.				
	Total	Protein	Fat	Carbohydrate	Lactose
Tube-Feeding Formula 1					
Evaporated skim milk	1,000	70	..	100	100
Skim milk powder	200	72	2	104	104
Egg yolks	100	16	32	1	...
Sugar	100	..	..	100	...
Salt *	3.5	..	..	...	...
Water and vitamin supplement †	...	..	..	...	...
Total	...	158	34	305	204
Total calories: 2,150					
Total volume: 1,500 cc.‡					
Tube-Feeding Formula 2					
Milk, whole	1,000	35	39	49	49
Skim milk powder	90	32	0.9	46.8	46.8
Eggs, whole	200	25.6	23	1.4	...
Dextri-Maltose No. 1	100	..	..	100	...
Cream, 20%	200	5.8	40	8	8
Salt *	3.0	..	..	...	...
Vitamin supplement †	...	..	..	...	...
Total	...	98	103	205	104
Total calories: 2,150					
Total volume: 1,500 cc.‡					

* The total sodium content for both formulas was approximately 150 mEq. per 1,500 cc. of formula.
† The vitamin supplement was Vitakon (Upjohn), 5 cc. for each 1,500 cc. of formula. This contained 2 mg. of thiamin, 3 mg. of riboflavin, 30 mg. of niacin, and 100 mg. of ascorbic acid.
‡ The volume of 1,500 cc. with a caloric value of 2,150 was the amount administered in twenty-four hours.

4. (*a*) Stare, F. J., and Thorn, G. W.: Protein Nutrition in Problems of Medical Interest, J. A. M. A. **127**:1120-1127 (April 28) 1945. (*b*) Jolliffe, N.; Tisdall, F. F., and Cannon, P. R., Editors: Clinical Nutrition, edited for Food and Nutrition Board, National Research Council, New York, Paul B. Hoeber, Inc., 1950. (*c*) Varco, R. L.: Preoperative Dietary Management for Surgical Patients with Special Reference to Lesions of the Stomach and Duodenum, Surgery **19**:303-378 (March) 1946. (*d*) Bridges, M. A.: Dietetics for Clinician, Ed. 4, Philadelphia, Lea & Febiger, 1941, pp. 216-218. (*e*) Wohl, M. G., Editor: Dietotherapy: Clinical Application of Modern Nutrition, Philadelphia, W. B. Saunders Company, 1945, pp. 870, and 980.

5. (*a*) Barborka, C. J.: Treatment by Diet, Ed. 5, Philadelphia, J. B. Lippincott Company, 1948, pp. 685-687. (*b*) McLester, J. S.: Nutrition and Diet in Health and Disease, Philadelphia, W. B. Saunders Company, Ed. 4, 1943, p. 742; (*c*) Ed. 5, 1949, p. 685; (*d*) Ed. 6, 1952, pp. 575-576. (*e*) Davidson, L. S. P., and Anderson, I. A.: A Textbook of Dietetics, Ed. 2, New York, Paul B. Hoeber, Inc., 1947, pp. 390-394. (*f*) Cooper, L. F.; Barber, E. M., and Mitchell, H. S.: Nutrition in Health and Disease, Ed. 8, Philadelphia, J. B. Lippincott Company, 1941, p. 384. (*g*) Jolliffe.[4b] (*h*) Varco.[4c] (*i*) Bridges.[4d] (*j*) Wohl.[4e]

disadvantages when actually administered. A comparison of the composition of some of the formulas recommended by these authors discloses that they vary over a wide range of possible combinations of the three major food constituents. For example, it was found that the daily carbohydrate content of the different formulas varied from 96 to 409 gm., that of protein from 60 to 140 gm., and that of fat from 14 to 177 gm. The total daily caloric content of the formulas also varied greatly.

Concerning the protein content, there seem to be no advocates of a low protein level. Rather, almost all authors recommend either a moderate or a high protein level. Stare and Thorn [4a] say: "There seems to be no advantage to protein intakes greater than 100 gm. per 24 hours unless there are unusual avenues of protein loss." Varco [4c] has developed and used extensively a high protein, low fat formula for the preoperative nutritional upbuilding of patients. McLester [6] also uses routinely a high protein level.

Aside from the allergic side-reactions manifested in those who are hypersensitive to particular proteins, we were unable to discover evidence in the literature to suggest that a very high protein diet will cause too frequent bowel movements. In discussing the problem of diarrhea in connection with preoperative nutritional care with the object of improving the protein status of the surgical candidate Varco [4c] does not relate composition of the formula to the appearance of the symptom but says "It is our impression that this problem [diarrhea] is minimal whenever the dispensing apparatus is maintained thoroughly clean or preferably sterilized."

It would seem that not much attention has been paid to possible adverse effects from the carbohydrate contained in formulas for tube feeding for human use. However, Bridges [4d] does have this to say: "The introduction of a diet too high in carbohydrate is not indicated. The customary oral digestion is self-evidently absent. Hence, the addition of too much carbohydrate may produce untoward symptoms." Furthermore, there is evidence, based on animal work, for a belief that possibly the character of the carbohydrate or its ratio to the other constituents of the dietary may cause adverse symptoms. Handler [7] studied the biochemical defect underlying the nutritional failure of young rats on diets containing large amounts of lactose and galactose. On basal diets containing 10% casein and 81% lactose groups of 10 rats failed to grow and died within 3 to 20 days. Handler considered that it was the galactose moiety of the lactose molecule which was responsible for the observed effects. He observed that the critical level of lactose in the diet appeared to be 60 to 70%, while that of galactose was 30 to 40%. Most rats had at least a moderate diarrhea when fed the lactose diets and a diarrhea of lesser extent when fed the galactose diets. Necropsy performed on rats which had been fed the lactose diet and the galactose diet showed their intestines to be greatly distended with gas and to contain heavy bacterial colonies. Roentgenograms revealed a complete failure of skeletal calcification in adolescent rats maintained on lactose or galactose.

Whittier and his co-workers,[8] in studying the effects of lactose on growth and longevity in rats with a view to establishing the value of lactose in infant feeding,

6. Footnote 5*b*, *c*, and *d*.

7. Handler, P.: The Biochemical Defect Underlying the Nutritional Failure of Young Rats on Diets Containing Excessive Quantities of Lactose or Galactose, J. Nutrition **33**:221-233 (Feb.) 1947.

8. Whittier, E. O.; Cary, C. A., and Ellis, N. R.: The Effects of Lactose on Growth and Longevity, J. Nutrition **9**:521-532 (April) 1935.

found that when the proportion of lactose reached levels of 45 and 63.5% all the rats experienced diarrhea and did not gain weight for about three weeks. The rats tolerated the same level of sucrose very well. At the end of this time, however, they recovered from the diarrhea and made good gains, in spite of the fact that they were consuming the large amounts of lactose. Another group of workers, Ershoff and Deuel [9] found that a particular strain of rats consistently experienced diarrhea, sometimes within 24 hours of the initial feeding, when fed either lactose or beta-lactose as the sole source of carbohydrate. The same trial on a different strain of rats failed to produce diarrhea after eight days of feeding.

Regarding the fat content, there seem to be two schools of thought: the one represented by McLester,[5c] who expresses the belief that fat per se is likely to cause diarrheal symptoms in the patient who is so extremely ill as to require nasal tube feeding, and the other school represented by Stare and Thorn,[4a] who see a great need for calories in these patients. Fat, being a most effective vehicle for supplying calories, is presented in liberal amounts. It is interesting to note that diarrhea was a symptom of sufficient importance to cause Stare and Thorn to include applesauce or some form of pectin as an antidiarrheal agent in their routine formula.

PLAN OF STUDY

In order to determine whether peculiarities of composition of the standard tube-feeding formula (designated "Formula 1" for purposes of this study) was the cause of the diarrhea which occurred in some patients or whether these patients would react similarly to any nutritious formula of equal caloric content and administered in the same amount and manner, a second formula was devised which was to be alternated with the first. This second diet was designated "Tube-Feeding Formula 2." The composition of both formulas is presented in Table 1. Formula 2 was designed to provide protein, carbohydrate, and fat in proportions much more closely resembling those of a normal diet than was the case with Formula 1. Also, its content of milk solids other than fat was much less than that of the latter formula. The total daily volume and the total daily caloric value of the two formulas were exactly the same, and their total daily mineral and vitamin contents were approximately the same.

A plan was set up whereby every second patient for whom nasogastric tube feedings were ordered at St. Marys Hospital during a period of seven months received Formula 1, whereas the alternate patients received Formula 2. Patients fed directly into the small intestine, either by means of an enteric stoma or by a nasal tube passed beyond the pylorus, were not included in this study. Also excluded were a few patients for whom physicians ordered special tube-feeding formulas differing from the two under consideration. Children were treated in the same manner as adults, but as a separate group. The amounts administered daily were smaller for the young children, being based on their caloric requirements. Thirteen of the 74 patients studied were children.

The diagnoses of patients for whom nasogastric feedings were ordered varied widely, but the great majority (about 73%) were patients who had sustained brain

9. Ershoff, B. H., and Deuel, H. J., Jr.: Inadequacy of Lactose and Beta-Lactose as Dietary Carbohydrates for the Rat, J. Nutrition **28**:225-234 (Oct.) 1944.

trauma or who were suffering from the effects of brain lesions (particularly tumors) either in the unoperated state or postoperatively. The later stages of the study included a number of poliomyelitis patients.

An attempt was made to standardize the manner of all tube feeding. The nurses responsible for feeding were requested to limit the amount of each feeding to 200 cc., with the interval between feedings to be not more than two hours, during the waking hours (usually 6:00 a. m. to 12:00 midnight). The feedings, previously warmed to body temperature, were given at a constant drip and were never allowed to run rapidly through the tube. The type of tube-feeding set long in use at St. Marys Hospital was employed throughout the study. This consisted of an arsphenamine (Salvarsan) flask and amber intravenous tubing which connected to a 14-gauge Levin tube. A Vacodrip and a clamp made it possible to regulate the rate of flow. The Levin tube was inserted by the physician either at the time of operation or when required for feeding purposes. Clogging of the tube or failure of the formula to flow through freely was not encountered as a problem in this study, as we considered it most important that any feeding to be tested should require a minimal amount of attention to the drip apparatus on the part of the nursing staff.

In order to secure necessary cooperation, full instructions concerning the purposes and plans of the study were supplied to all hospital personnel involved—that is, physicians, nurses, and dietitians. In general, the cooperation received was excellent. In a few instances there was some reluctance on the part of physicians and nurses to conform strictly to the program of alternation, for doing so, they felt, might induce a debilitating diarrhea, a risk too great to be taken by the seriously ill patient under their care. In addition, a few cases could not be included in this study because of failure on the part of those caring for the patient to administer the feedings according to the suggested schedule.

The only measuring stick of the relative value of the two formulas being studied was the incidence of diarrhea during their use. Though the symptom "diarrhea" would seem to be a vague and indefinite measuring stick for a controlled study, in actual experience it proved to be quite sharply definitive. A patient who passed four or more watery stools in 24 hours was considered to have diarrhea. In those patients who experienced diarrhea the number of stools was usually considerably greater than this and their passage began within a few hours of the first feeding. According to the original plan of the study, it was expected that the offending formula would be administered for two or three days after the appearance of diarrhea. In actual practice, this had to be abandoned, and the alternative formula was substituted as soon as possible after diarrhea developed. If the formula originally administered to a patient was well tolerated, no change in formula was effected. Although it would have been desirable from the standpoint of our study to administer both formulas to all patients, we were reluctant to change a satisfactory therapeutic program at the risk of inducing a diarrhea in seriously ill patients.

An attempt was made to prevent the administration of camphorated opium tincture (Paregoric), kaolin and pectin (Kaopectate), or other medication to relieve diarrhea. However, such medications were used in a few instances, but it was our impression that the diarrhea almost always persisted in spite of medication, until the formula was changed. Data from patients who required nasal tube feeding for

less than three full days were not included. Craniotomy patients usually required tube feeding for periods ranging from five days to two weeks. A few long-term patients were maintained for several weeks, the longest period being nine weeks.

One of us (Smith) regularly prepared and delivered both formulas to the refrigerators and visited at least once daily each patient receiving tube feeding. Information concerning each patient was recorded on a form drawn up for the purpose. Such factors as total intake of fluid, output of urine, nature and number of stools, medication, and changes in the patient's therapeutic program were noted. The patient's protein and caloric intake for the previous day was charted daily. During the latter half of the study the staff of the central nourishment room of the hospital prepared and delivered the feedings.

RESULTS AND COMMENT

A tabulation of the results is presented in Table 2. This clearly shows that Formula 2 was much better tolerated than Formula 1. The difference between the two is even more striking when it is realized that 10 of the 27 patients who took Formula 2 without experiencing diarrhea had previously experienced this symptom when taking Formula 1. Furthermore, these 10 patients tolerated Formula 2 even

TABLE 2.—*Results in 74 Patients of Two Formulas for Tube Feeding*

Type of Feeding	Patients Studied, No.	Occurrence of Diarrhea	
		Patients, No.	%
Formula 1	44	17 *	38.6
Formula 2	30	3 †	10.0

* Five of these patients were children.
† Two of these patients were children and the third was an adult with a colonic stoma.

though they were experiencing diarrhea when they started taking it. Two of the three patients who experienced diarrhea when taking Formula 2 had also experienced this symptom when taking Formula 1.

Although other factors which might cause diarrhea could not be eliminated from a study such as this, involving patients of all age groups and varying nutritional states, with a wide diversity of illnesses, many of whom had undergone recent operations and many of whom were taking medications of various kinds, there was no reason to believe that such factors were more frequent or prominent in the group of patients taking Formula 1 than in that taking Formula 2. For these reasons the difference in incidence of diarrhea between the two groups can be related significantly to the difference in composition between the two formulas.

Attempts to determine whether patients might develop a tolerance, after having earlier shown a lack of tolerance to Formula 1 were not carried out with a sufficiently large number of patients to give conclusive results. The first patient studied did not tolerate the second trial. The second and third patients experienced no diarrheal symptoms when Formula 1 was administered a second time.

While it was not deliberately intended to test Formula 1 in patients who had been reacting favorably toward Tube-Feeding Formula 2, this trial was made accidentally in one case, owing to a mistake being made in the ordering of the formula. There was sudden onset of diarrhea within six or eight hours of the first feeding.

Whether the diarrhea which occurred so frequently among patients taking Formula 1 was caused by the high proportion of protein or carbohydrate, the nature of the carbohydrate, the unbalanced distribution of food constituents in the offending formula, or some other factor is not apparent from this study. Although the value of a "balanced dietary" is common knowledge, there is little, if any, evidence in the literature of investigations of the consequences of unbalanced mixtures in the human being. An analysis of the comparative lactose contents of the two diets, as seen in Table 1, shows that the standard formula contains approximately twice as much as Tube-Feeding Formula 2. While 200 gm. of lactose is probably more than is ever found in a normal day's meals, it is still not of the order of the amounts fed to the rats in Handler's experiments.

Formula 1 was devised at a time when there was particular interest in the problem of prevention and correction of protein depletion among medical and surgical patients. For this reason its protein content was made unusually high. The reason for its low fat content is not now clearly apparent, though it seems probable that fat was expected to be poorly tolerated by some patients. This expectation was not confirmed by the results of the present study, since Formula 2, which was well tolerated, contained approximately three times the amount of fat contained in Formula 1, which was poorly tolerated. Whether a diet which is extremely high in protein (such as Formula 1) is any more effective in preventing or correcting protein depletion than is a diet which contains a moderately large amount of protein (such as Formula 2) is a question to which there is not yet a completely satisfactory answer. Among all the available information which bears on this question there is a considerable amount of evidence to suggest that there is no advantage to a very high protein diet.[10] Indeed, some observers [11] have expressed the belief that the practice of forcing the body to dispose of large amounts of nitrogenous products may simply be an added form of stress to an already handicapped organism. In the specific case of Formula 1 used in this study, the doubtful advantages of its very high protein content seemed to be greatly outweighed by the distinct disadvantage of the frequency with which diarrhea developed when it was being administered. Whether other high protein formulas would be any better tolerated, we do not know.

SUMMARY AND CONCLUSIONS

Because of the frequent occurrence of diarrhea among patients taking a standard tube-feeding formula high in protein and carbohydrate and low in fat, a controlled clinical study was carried out to obtain information concerning the incidence and possible causes of this symptom. In order to determine whether the diarrhea was due to peculiarities in composition of the standard formula (Formula 1) or whether patients would react similarly to any nutritious mixture of equal caloric content and administered in the same amount and manner, a second formula (Formula 2) was devised, which provided protein, carbohydrate, and fat in proportions more closely resembling those of a normal diet than was the case with Formula 1. All patients

10. Howard, J. E.: Metabolic Observations on Patients Convalescent from Fracture, Tr. A. Am. Physicians **58**:162-170, 1944.

11. Peters, J. P.: Symposium on Physiological Aspects of Convalescence and Rehabilitation: Problems of Nitrogen Metabolism, Fed. Proc. **3**:197-201, 1944-1945. Moore, F. D.: Surgical Nutrition, Nutrition Rev. **6**:161-164 (June) 1948.

at St. Marys Hospital for whom nasogastric tube feedings were ordered during a period of seven months received either Formula 1 or Formula 2 in a regular system of alternation. The manner of administration of all tube feedings was standardized.

Diarrhea occurred in approximately 39% of the 44 patients who took Formula 1 and in only 10% of the 30 patients who took Formula 2. Ten of the 12 patients who took both feeding mixtures experienced diarrhea when taking Formula 1 but had none with Formula 2. The other 2 patients were intolerant to both formulas.

The cause of the poor tolerance of Formula 1 is not evident from this study but apparently is related to some characteristic of the composition of the feeding mixture. Qualities of Formula 1 which might be of significance in this respect either alone or in combination are (1) its high protein or carbohydrate content, (2) the nature of its high protein and carbohydrate content (largely derived from milk), and (3) its unbalanced composition in respect to the three major foodstuffs.

The frequency with which diarrhea developed when Formula 1 was being administered was a disadvantage which seemed greatly to outweigh the questionable advantages this formula may possess in preventing or correcting protein depletion by virtue of its very high protein content. Formula 2 was found to be a very satisfactory feeding mixture for routine use for patients who require nasogastric tube feedings.

NEEDLE LIVER BIOPSY IN THYROTOXICOSIS

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THERE are numerous reports in the literature concerning abnormal hepatic function and pathologic changes in the liver of patients with thyrotoxicosis. As a result, there is prevalent a notion that the liver is frequently involved by the thyrotoxic state, both functionally and structurally. It is to be noted, however, that the clinical data are quite inadequate or scanty in most, if not all, series of cases reported as demonstrating anatomical abnormalities in the liver of such patients. Moreover, the pathologic changes as described are the ones observed exclusively in the autopsy material. Thus, the possibility that such abnormalities might be due to some complicating or coexistent conditions has not been adequately ruled out. Also it is obvious that the pathologic changes in the liver as described have been seen only in those patients who were so gravely ill as to die, either from the hyperthyroid state per se or from complications or entirely unrelated conditions. It would be interesting to know whether or not the liver is actually involved in an "average" patient with thyrotoxicosis who, as is usually the case nowadays, survives the ordeal of both the illness and the surgical treatment. This question is also of interest to the surgeon, who well knows the added risk of a major surgical procedure in a patient with an abnormal liver.

We decided to investigate this question in living patients by performing liver aspiration biopsies and correlating anatomical material thus obtained with the results of a battery of hepatic function tests. The presentation of our data will follow a brief review of the literature reporting the association of hepatic derangement with the thyrotoxic state.

Whereas the thyroid gland profoundly influences the body economy in its many aspects, such as the rate of metabolism, the processes of anabolism and catabolism, and the reactivity of the sympathetic nervous system, as well as affecting the activity of other endocrine glands, the liver closely vies with the thyroid gland in the production of similarly far-reaching effects through the multiplicity of hepatic functions, metabolic and otherwise. The functions of the liver include the break-

The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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down of the very hormone, thyroxin, by means of which the thyroid gland wields its influence on the body. One could well expect that the two organs, their metabolic pathways crossing at many points in the great pool of energy exchanges in health, would influence each other markedly also in disease. In fact, frequent association of both functional and anatomical changes in the liver with thyrotoxicosis has been repeatedly called to the attention of clinicians since it was first mentioned by Paul [1] in 1865.

Lichtman [2] has thoroughly reviewed the experimental evidence of the deleterious effect of thyrotoxicosis on the liver. The interested reader is referred to Lichtman's authoritative volume for details on this subject. Here it will suffice to say that animal experiments have apparently disclosed the following facts: (1) depletion of glycogen content of the liver on feeding excessive doses of thyroid gland and (2) various anatomic changes in the liver, such as parenchymatous or fatty degeneration or central lobular necrosis, in experimental hyperthyroidism, particularly in animals with bacterial infections or in animals fed a diet deficient in vitamin B complex.

Numerous reports of disturbances of liver function and pathologic changes in the liver in association with thyrotoxicosis in man have also appeared in the literature. Again, we do not propose to attempt a comprehensive review, but some of the most significant reports will be briefly mentioned.

Clinical observations interpreted as indicating hepatic involvement presumably due to the hyperthyroid state, as particularly suggested by occasional patients with jaundice, along with definite pathologic changes found in the liver at autopsy, have stimulated extensive studies of liver function.

Impairment of hepatic function has been noted by many workers employing various liver function tests: the phenoltetrachlorphthalein and sulfobromophthalein (bromsulphalein®) dye excretion test; the cinchophen oxidation test; the oral hippuric acid test; the Takata-Ara reaction; Hanger's cephalin-cholesterol flocculation test; determinations of plasma proteins, plasma prothrombin, serum phosphatase, and blood cholesterol, and tests of carbohydrate metabolism with oral galactase, glucose, and levulose tolerance curves.

Bauer, who introduced the galactose tolerance test, found pathologic galactosuria in patients with hyperthyroidism.[3] Maclagan and Rundle [4] reported that in 30 of 41 cases of thyrotoxicosis there was definite impairment of glycogen function. Althausen, Lockhart, and Soley [5] suggested that pathological galactosemia observed in hyperthyroidism is most probably due to rapid absorption of ingested galactose from the bowel. On the other hand, the results of application of the intravenous

1. Paul, cited by Shaffer, J. M.: Diseases of the Liver in Hyperthyroidism, Arch. Path. **29**:20, 1940.

2. Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts, Ed. 2, Philadelphia, Lea & Febiger, 1949.

3. Bauer, R.: Weitere Untersuchungen über alimentäre Galaktosurie, Wien. med. Wchnschr. **66**:2537, 1906.

4. Maclagan, N. F.; Rundle, F. F.; Collard, H. B., and Mills, F. H.: Liver Function in Thyrotoxicosis, Quart. J. Med. **9**:215, 1940.

5. Althausen, T. L.; Lockhart, J. C., and Soley, M. H.: New Diagnostic Test (Galactose) for Thyroid Disease, Am. J. M. Sc. **199**:342, 1940.

galactose test suggested to Stenstam [6] that, while peroral galactosuria is dependent upon increased intestinal absorption, abnormal galactosemia is frequently also the result of hepatic insufficiency. It is rather difficult to relate the results of glucose tolerance tests in patients with hyperthyroidism definitely to liver damage, because thyrotoxicosis itself may give rise to decreased sugar tolerance, although there is a temptation to attribute this to failure of glycogen storage in the liver. Adler and Lemmel [7] discovered an abnormal decrease in the blood cholesterol esters. It will be recalled that blood cholesterol values may be abnormal in hepatitis. Maddock, Collier, and Pedersen [8] found sulfobromophthalein dye retention of above 10% in 8 of their 13 patients with thyrotoxicosis. They thought that there was some parallelism between the severity of the hyperthyroid state, as measured by the basal metabolic rate, and impairment of liver function, as indicated by this particular test. In five patients with normal sulfobromophthalein tests the basal metabolic rate averaged +33% as compared with an average of +54% in eight patients who showed abnormal retention of the dye. A number of investigators reported a correlation of the excretion of hippuric acid with the basal metabolic rate and the cholesterol content of blood in cases of thyrotoxicosis.[9] Allison [9b] found Hanger's cephalin-cholesterol flocculation test to be positive in 13 out of 47 cases. In 11 cases 2+ values were obtained, and 3+ values in 2 cases. Hypoalbuminemia was observed in 63% of a group of patients with thyrotoxicosis by Bartels [10] and in 15 patients out of 24 by Brown and Mecray.[11] Lord and Andrus [12] found the level of plasma prothrombin not to be significantly altered before operation; in patients with thyrotoxicosis, a significant fall, however, occurred in 29 out of 36 patients postoperatively. It must be recalled the hypoprothrombinemia may follow many different major surgical procedures.

There is a lack of general agreement by the various investigators regarding the incidence of hepatic impairment in thyrotoxicosis. Lichtman [2] summarizes the evidence by stating that "Employing the various clinical liver function tests, 45 to 90 per cent of all cases of hyperthyroidism show some functional impairment, usually of slight to moderate degree." He is inclined to believe that "The cinchophen oxidation, the hippuratic acid synthesis, the galactose tolerance test and the plasma prothrombin level constitute the best methods for evaluating liver function in this

6. Stenstam, T.: Peroral and Intravenous Galactose Test, Lund, Håkan Ohlssons Boktryckeri, 1946.

7. Adler, A., and Lemmel, H.: Zur feineren Diagnostik der Leberkrankheiten: Cholesterin und Cholesterin-Ester im Blute Leberkranker, Deutsches Arch. klin. Med. **158**:173, 1928.

8. Maddock, W. G.; Collier, F. A., and Pedersen, S.: Thyroid Crisis: Its Relation to Liver Function and Adrenalin, West. J. Surg. **44**:513, 1936.

9. (*a*) Haines, S. F.; Magath, R. B., and Power, M. H.: Hippuric Acid Test in Hyperthyroidism, Ann. Int. Med. **14**:1225, 1941. (*b*) Allison, A.: Liver Damage in Thyrotoxicosis with Special Reference to the Results of Liver Function Tests in Patients Treated with Thiouracil, Glasgow M. J. **30**:417, 1949.

10. Bartels, E. C.: Liver Function in Hyperthyroidism as Determined by Hippuric Acid Test, Ann. Int. Med. **12**:652, 1938.

11. Brown, R. B., and Mecray, P. M.: Serum Proteins Before and After Operations for Hyperthyroidism, Endocrinology **22**:302, 1938.

12. Lord, J. W., Jr., and Andrus, W. DeW.: Changes in Liver Associated with Hyperthyroidism, with Study of Plasma Prothrombin Levels in Immediate Postoperative Period, Arch. Surg. **42**:643, 1941.

disease." In the opinion of some workers, the galactose tolerance test, generally speaking, is to be considered as one of the most reliable methods of detecting the presence of acute hepatocellular damage.[13] Lichtman [2] states that the galactose tolerance test appears to give the results "which can be more uniformly correlated with clinical criteria of severity of thyrotoxicosis, such as weight loss, duration of the disease and basal metabolic rate."

The evidence of anatomical changes in the liver of patients with hyperthyroidism has been as ample as that of functional hepatic impairment. Following the original pathologic report by Paul [1] there were many others. Marine and Lenhart [14] found in five of six autopsied patients with thyrotoxicosis well-marked thickening of the Glisson's capsule throughout the liver and made a diagnosis of atrophic cirrhosis in four patients. Kerr and Rusk [15] reported acute yellow atrophy associated with hyperthyroidism. Kerr [16] also reported the presence of extensive hepatic fibrosis in this disease. Beaver and Pemberton,[17] in a detailed study of the pathologic anatomy of the liver in 107 cases of exophthalmic goiter, found three types of hepatic lesions which they attributed to thyrotoxicosis: (1) acute degenerative changes (fatty metamorphosis, focal and central necrosis, and circulatory stasis); (2) simple atrophy, and (3) subacute toxic atrophy and toxic cirrhosis. Weller [18] excluded from his series of 61 autopsies of patients with exophthalmic goiter 13 in which factors known to be significant in the production of hepatitis were present. In the remaining 48, the author felt that "no known cause of hepatitis existed other than the possibility that it might be due to thyrotoxicosis." In this group he observed structural changes in the liver varying from slight degrees of chronic hepatitis to a widespread and necrotizing process which, in his opinion, could be considered as representing acute yellow atrophy. Well-marked hepatitis was found in 54% of this group of 48 patients, whereas "a matched control survey of the same size yielded but a single case (2%) with a well-marked hepatitis." Cameron and Karunaratne,[19] in a series of 30 autopsied patients with exophthalmic goiter, found the liver to be frequently damaged by fatty changes, sometimes amounting to acute necrosis, local or general atrophy, and cirrhosis, or by any combination of these. They thought that it was reasonable to regard these changes "as representing reactions to varying grades of injury the result of thyroid derangement." Shaffer [20] noted fatty infiltration of the liver in 92% of 24 patients with thyrotoxicosis. How-

13. Bockus, H. L., and Monaghan, J. F.: The Influence of Thyroid Disease on the Liver, in Bockus, H. L., and others: Gastro-Enterology, Vol. 3, Philadelphia, W. B. Saunders Company, 1946.

14. Marine, D., and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter: The Anatomical and Physiological Relations of the Thyroid Gland to the Disease; the Treatment, Arch. Int. Med. **8**:265, 1911.

15. Kerr, W. J., and Rusk, G. Y.: Acute Yellow Atrophy Associated with Hyperthyroidism, M. Clin. North America **6**:445, 1922.

16. Kerr, W. J.: Necrosis of Heart and Liver in Thyrotoxicosis, with Some Notes on Possible Changes in Other Organs, Northwest Med. **29**:430, 1930.

17. Beaver, D. C., and Pemberton, J. deJ.: The Pathologic Anatomy of the Liver in Exophthalmic Goiter, Ann. Int. Med. **7**:687, 1933.

18. Weller, C. V.: Hepatic Pathology in Exophthalmic Goiter, Ann. Int. Med. **7**:543, 1933.

19. Cameron, G. R., and Karunaratne, W. A. E.: Liver Changes in Exophthalmic Goitre, J. Path. & Bact. **41**:267, 1935.

20. Shaffer, J. M.: Diseases of the Liver in Hyperthyroidism, Arch. Path. **29**:20, 1940.

ever, he was also able to find fatty changes in 56% of a carefully selected control group of 100 patients, 50 of whom died from trauma. However, while acknowledging the fact that such fatty changes thus commonly occur in many conditions other than hyperthyroidism, he was impressed with the greater frequency and severity of hepatic changes which occurred in the group with thyroid dysfunction and concluded that "The high percentage of association together with the severity of the changes makes it impossible to ignore them." Moschcowitz [21] found 11 patients with hepatic cirrhosis in a group of 31 autopsied patients with diffuse toxic goiter or exophthalmic goiter (35.5%). He felt that the changes in the liver which he observed represented "a type of hepatic cirrhosis apparently pathognomonic of diffuse goiter." The lesion was identical in both form and progression with that seen in chronic hepatic venous congestion and cardiac cirrhosis but differed from the latter in that topographically it was not around the central vein but in the interlobar septums, in addition frequently encroaching on the lobule itself. Moschcowitz felt that pathogenetically the lesion was the result of increased velocity of blood flow usually observed in thyrotoxicosis, the altered circulatory dynamics rendering the maintenance of the normal pressure relations between the hepatic artery and the portal vein difficult, thus finally giving rise to decompensation with resultant stasis in these areas. In time, just as in chronic venous congestion of central origin, capillary sclerosis resulted, with eventual fibrosis. In the early phases the areas of fibrosis could be traced to the terminal ramifications of the hepatic artery as it passes into the interlobular vascular septums. The cirrhosis is further distinguished by the fact that it exists predominantly in the subcapsular zone of the liver. As in the ordinary congested liver, this is due to the resistance offered by the capsule of the liver. Wallerstein and Walker [22] reported a case of thyrotoxicosis with evidence of marked liver damage and hepatosplenomegaly in which improvement of hepatic function and disappearance of splenomegaly followed subtotal thyroidectomy. Moderate enlargement of the liver was reported by Bickel [23] to occur in approximately 40% of patients with hyperthyroidism.

Some investigators have gone so far as to postulate that the disturbed liver physiology plays an important role in the development of thyroid crisis and in fact is responsible for death in this condition.[20] However, Foss, Hunt, and McMillan,[24] on careful investigation of this problem in a series of 29 autopsied patients who presumably died from thyroid disease, came to the conclusion that in 9 instances death was due to associated conditions rather than to the thyroid disease, that in 9 other cases in which a clinical diagnosis of thyroid crisis was made the autopsy revealed that death was really due to an overwhelming infection which antedated the symptoms of crisis, and that this left only 11 patients who could rightfully be considered as having died in true thyroid crisis. However, the pathologist was unable to explain the pathogenesis of crisis. Although there were varying degrees of hepatic necrosis present, the authors failed to find any correlation between

21. Moschcowitz, E.: Pathogenesis of Cirrhosis of the Liver Occurring in Patients with Diffuse Toxic Goiter, Arch. Int. Med. **78**:497, 1946.

22. Wallerstein, R. S., and Walker, W. J.: Hepatosplenomegaly and Liver Damage in Graves's Disease, Ann. Int. Med. **31**:904, 1949.

23. Bickel, G.: Les cirrhoses hepatiques d'origine thyroïdienne, Schweiz. med. Wchnschr. **73**:1160, 1943.

24. Foss, H. L.; Hunt, H. F., and McMillan, R. M.: The Pathogenesis of Crisis and Death in Hyperthyroidism, J. A. M. A. **113**:1090, 1939.

the degree of hepatic injury and the severity of the clinically observed state. They felt that the condition ordinarily designated as "thyroid crisis" was as yet but poorly understood. McArthur, Rawson, Means, and Cope [25] more recently confirmed the above conclusions. They observed a paucity of any significant pathologic changes in the liver in one half of their series of 24 patients who died in the state recognized by the clinicians as thyroid crisis. Chronic passive congestion was seen in two patients, central necrosis in one, and fatty metamorphosis in one. Postmortem examination disclosed the frequent occurrence of cardiac and pulmonary pathologic conditions. The authors felt that the precipitating factors identifiable as provocative of thyrotoxic crisis included the operative procedure itself (thyroidectomy), pneumonia, iodine withdrawal, postoperative hemorrhage and secondary suture, wound sepsis, and digitalis intoxication. They concluded that thyroid storm was "a syndrome of many facets and not a specific entity."

Thus cursory review of the literature seems to indicate that three main types of pathologic changes in the liver of patients with thyrotoxicosis have been encountered: (1) acute degeneration represented by marked fatty change and actual focal or central necrosis, (2) local or general atrophy, and (3) cirrhosis, perhaps of the specific type, as described by Moschcowitz.[21] It appears that fatty changes probably represent the most common type of hepatic involvement described in this disease. Depending on whether one views these fatty changes as representing a process of infiltration or of degeneration, one would be apt to ascribe them to the increase in metabolic demands of the hyperthyroid state or to the directly acting toxic effect, respectively.[13]

The pathogenesis of liver damage believed to be due to thyrotoxicosis is said not to have been definitely established, but there is no paucity of theories on this subject. The glycogen depletion in the liver was thought to reflect a physiologic manifestation of the increase in metabolic demands of the hyperthyroid state.[2] As carbohydrate stores are exhausted, protein stores are also drawn upon for their carbohydrate contribution. Depletion of glycogen and protein stores may put the liver in a precarious position, thus depriving it of the all-important protective mechanism against damage. Himsworth [26] suggests that the liver injury in thyrotoxicosis is due to a relative deficiency of such factors as cystine, methionine, and tocopherol, the deficiency being conditioned by increased metabolism. This theory is supported by the experimental work of György and Goldblatt,[27] who found that by adding 0.1% thiouracil to a cirrhosis-producing diet they were able to prevent the development of hepatic necrosis in rats. Himsworth [26] also suggested that the increase of oxygen requirements of the liver in hyperthyroidism may create a state of relative anoxia leading to central lobular necrosis. Infection may also play a role by accentuating the relative dietary deficiency through the aggravation of the hyperthyroid state or the increase of metabolism consequent on pyrexia.[9b] Moschcowitz' [21] theory of circulatory decompensation of local origin in the liver as being responsible for the cirrhosis in association with thyrotoxicosis has already been mentioned.

25. McArthur, J. W.; Rawson, R. W.; Means, J. H., and Cope, O.: Thyrotoxic Crisis, J. A. M. A. **134**:868, 1947.

26. Himsworth, H. P.: Lecture on the Liver and Its Diseases, Oxford, Blackwell Scientific Publications, 1947.

27. György, P., and Goldblatt, H.: Thiouracil in Prevention of Experimental Dietary Cirrhosis of Liver, Science **102**:451, 1945.

It is to be emphasized that all the above-mentioned reports of liver pathology in hyperthyroidism have been based exclusively on autopsy material. In other words, the hepatic changes have been described only in those patients who were ill enough to die, either from thyrotoxicosis per se or from such complicating factors as infection, operation, or associated disturbances in other glands of internal secretion, as in diabetes. Thus perusal of the literature may possibly give an erroneous impression of what can actually be expected as regards the state of the liver in an average patient who survives. We decided to investigate this question in living patients by performing liver aspiration biopsies. In the course of our investigation we also found that a similar study had been recently carried out in Denmark by Piper and Poulsen.[28] The results of their research will be mentioned later along with the discussion of our own material.

METHODS

In addition to the basal metabolic rate, which was determined for every patient, plasma protein bound iodine was determined in most patients. Liver function tests consisted of serum bilirubin, serum gamma globulin, serum proteins with albumin/globulin ratio, cephalin cholesterol flocculation, thymol turbidity, sulfobromophthalein dye excretion, and plasma prothrombin. Biopsy specimens of the liver were obtained by use of the Vim-Silverman needle. The specimens were fixed immediately in 10% formalin, in alcohol and, after the usual tissue mat inbedding, they were cut at 6 μ and stained with hematoxylin and eosin and then by Lillie's modification of the Bauer method.[29] Duplicate slides in several instances were digested with diastase prior to the application of the Lillie-Bauer stain. The technique recommended by Mallory[30] was employed for the demonstration of reticulum fibers.

CLINICAL MATERIAL

Thirteen patients with thyrotoxicosis were studied. Their ages ranged from 23 to 61. The duration of illness was estimated to range from 3 to 36 months. Two patients (Cases 2 and 6) had subtotal thyroidectomies four years prior to admission. In both these patients the recurrence of thyrotoxic symptoms occurred 36 months before entry. In only two patients in this series was thyrotoxicosis complicated by other conditions. In one of these (Case 10) there was present possibly a slight degree of myocardial insufficiency; in the other (Case 12) diastolic hypertension was found along with adrenocortical carcinoma discovered in the course of routine investigation of the hypertensive state. One patient (Case 1) received propylthiouracil, 100 mg. daily, for a period of 12 months but had no therapy for about a month prior to the performance of liver biopsy. Another patient (Case 2) was also treated for some time for recurrence, but no information was available as to the precise medication administered; the patient discontinued treatment four months prior to liver biopsy. One patient (Case 3) received iodides for a period of four months but discontinued treatment two months prior to liver biopsy. Another (Case 6) also received some medication before admission but had no therapy for 10 months prior to liver biopsy.

RESULTS

All the laboratory data are recorded in Table 1. It can be seen at a glance that only in 3 of the 13 patients were the results of liver function tests abnormal; the cephalin cholesterol flocculation tests were 4+ and 3+ in Cases 5 and 6, respectively; serum bilirubin was 1.7 mg. per 100 cc. in Case 12.

28. Piper, J., and Poulsen, E.: Liver Biopsy in Thyrotoxicosis, Acta med. scandinav. **127**: 439, 1947.

29. Lillie, R. D.: Histopathologic Technic, Philadelphia, The Blakiston Company, 1948, p. 145.

30. Mallory, F. B.: Pathological Technique, Philadelphia, W. B. Saunders Company, 1938, p. 163.

Observations made on the individual biopsy specimens are summarized in Table 2. The parenchymal liver cells were of fairly uniform size except in two cases in which the variation was slightly more than the usual. Cytoplasmic vacuoles indicating fatty metamorphosis were encountered in only one instance (Case 8). There was no dissociation of liver cells. Glycogen content was reduced throughout all

TABLE 1.—*Result of Liver Function Tests in 13 Patients with Thyrotoxicosis*

Case	Age, Yr.	Duration of Illness, Mo.	BMR	Plasma Protein Bound Iodine, γ/100 Cc.*	Serum Bilirubin, Mg./100 Cc.	Serum Gamma Globulins, Mg./100 Cc.	Serum Proteins, Gm./100 Cc.			Cephalin Cholesterol Flocculation (48 Hr.)	Thymol Turbidity (Units)	Sulfobromophthalein Retention, % in 45 Min. (Dose, 5 Mg./Kg.)	Plasma Prothrombin Time (% of Normal Control)
							Total	Albumin	Globulin				
1	23	14	+44	11.9	0.6	.....	7.6	5.1	2.5	+	6	3	100
2	28	36	+49	11.6	0.6	1,080	7.1	4.7	2.4	++	5	1	100
3	36	10	+68	....	...	720	7.3	5.2	2.1	+	3	0	...
4	36	5	+75	10.3	...	.....	6.6	4.5	2.1	+	3	2	100
5	32	4	+37	....	1.2	780	7.3	4.8	2.5	++++	3	0	100
6	27	36	+52	†	0.5	240	6.2	4.5	1.7	+++	3	1	100
7	29	24	+52	13.4	0.5	1,660	6.2	4.6	1.6	+	3	5	100
8	35	3	+49	9.7	0.7	1,020	6.8	4.1	2.7	+	3	2	100
9	58	4	+36	....	0.6	.....	...	...	...	±	3	0	100
10	60	3	+87	10.8	1.1	480	5.7	4.0	1.7	+	3	0	100
11	61	10	+32	8.8	1.0	900	6.5	4.8	1.7	—	3	5	92
12	25	12	+39	9.1	1.7	660	5.8	4.5	1.3	+	3	4	88
13	40	6-12?	+80	19.2	0.8	900	6.8	4.4	2.4	+	3	5	100

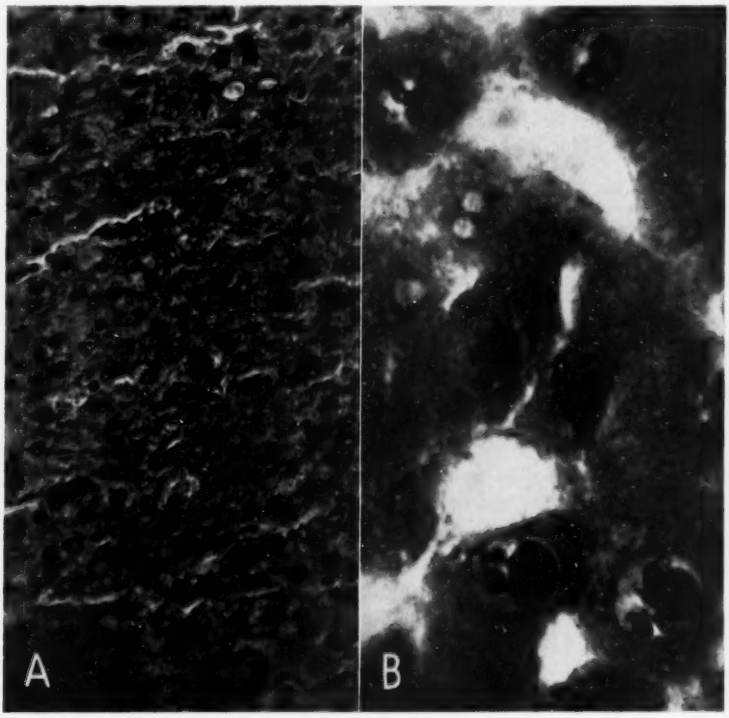
* This determination was done at the University of California School of Medicine. Normal range: 4 to 8 γ per 100 cc.
† Radioactive iodine uptake, —54%.

TABLE 2.—*Results of Liver Biopsy in 13 Patients with Thyrotoxicosis*

Case	Liver Biopsy Findings
1	Central veins moderately engorged; slight increase of portal connective tissue, with extension into midlobular zone
2	Moderate variation in the size of the liver cell nuclei with ballooning of the nuclei throughout all lobular zones
3	Moderate variation in size of the liver cell nuclei
4	Glycogen content of liver cells reduced
5	A few eosinophilic leucocytes in portal areas
6	Moderate variation in the size of the liver cell nuclei; moderate number of binucleated liver cells and occasional vacuolization of nuclei; slight eosinophilic infiltration of portal areas
7	Slight variation in size of liver cell nuclei
8	Slight cytoplasmic vacuolization of liver cells indicating fat deposit; moderate variation in the size of the liver cell nuclei; nuclei of peripheral liver cells frequently ballooned and containing a few granules staining positively with Bauer-Lillie stain
9	Moderate variation in the size of liver cell nuclei and frequent ballooning of nuclei in peripheral and midlobular zones, with occasional granule staining positively with Bauer-Lillie stain; some binucleated liver cells
10	Moderate variation in the size of the liver cell nuclei
11	Moderate variation in the size of the liver cell nuclei
12	Moderate number of ballooned nuclei in peripheral liver cells; numerous clumps and granules in vacuolated nuclei, staining positively with Bauer-Lillie stain
13	Reduced glycogen content of liver cells throughout all zones; occasional ballooned liver cell nucleus with small granules staining positively with Bauer-Lillie stain

zones in two patients (Cases 4 and 12). In all the others an abundant amount of glycogen was demonstrated by the Lillie-Bauer stain. The perisinusoidal spaces (Disse space) were closed. The Kupffer's cells were not remarkable. Distention of the central veins was noted in Cases 1 and 6. In Case 6 it was associated with a recent perivascular hemorrhage, which might have been incidental to the perform-

ance of liver biopsy. In this specimen also a few eosinophilic leucocytes were seen in the portal spaces. In the other twelve biopsy specimens the portal areas were not remarkable. The reticulum stain revealed intact axial fibers. The cross fibers could not be recognized. In Case 1 several heavy positively staining fibers extended to the midlobular zone. Of greater interest was the appearance of the nuclei of the parenchymal liver cells. In five instances there was variation in the size of the nuclei beyond the usual degree, in four of which ballooning of the nuclei was noted (Cases 2, 6, 8, and 9). In two additional patients (Cases 12 and 13) the same nuclear vacuolization was observed. These changes were particularly striking in Cases 2, 9,



A (Case 4), liver biopsy specimen. Hematoxylin and eosin stain; × 190. Ballooning of liver cell nuclei in all zones of the liver lobule. *B* (Case 12), liver biopsy specimen. Bauer-Lillie stain; × 1,200. Note intranuclear clumps of positively staining material.

and 12, in which vacuolated nuclei were seen not only in the periphery of the lobules but also in the intermediate and central zones (Fig., *A*). In addition, in Cases 8, 9, 12, and 13 granules staining positively with Bauer-Lillie stain were also noted in the nuclei. This was most marked in Case 12 (Fig., *B*).

Thus the incidence of nuclear changes is rather high in our series, and, if one takes into consideration the possible influence of the thyrotoxic state on carbohydrate metabolism, this finding should not be discarded without further study. Vacuolization of the nuclei, assumed to represent infiltration with glycogen, first reported by

Ehrlich,[31] was shown by Warren[32] to be related to the state of carbohydrate metabolism in patients with diabetes mellitus. Chipps and Duff[33] questioned the significance of this phenomenon, as they found a high incidence of nuclear vacuolization in their unselected series of autopsied patients. However, their conclusions perhaps can be discounted for two reasons: 1. The divergence between the results of study of liver morphology in autopsy material and in biopsy specimens has been stressed by Popper[34] and others. 2. In several extensive series of liver biopsies comprising more than 1,200 cases (the series of Popper and Franklin,[35] Klatskin and Yesner,[36] and Yesner and Kunkel[37]) the ballooning of the nuclei was noted in only three biopsies (from patients with diabetes mellitus, portal cirrhosis, and infectious hepatitis).

It will be noted that there is no correlation between the changes above described and the results of liver function tests. Thus, of the two cases with positive cephalin cholesterol flocculation tests, the biopsy in one (Case 5) was entirely within normal limits; in the other (Case 6), in which biopsy showed nuclear vacuolization, the cephalin cholesterol flocculation test was 3+ in 48 hours. In the remaining four cases exhibiting ballooning of the nuclei, the only remarkable pathological finding discovered (in addition to nuclear granules staining positively with Bauer-Lillie stain), liver function tests were all normal. Unfortunately tests of carbohydrate metabolism have not been included in the battery of liver function tests employed by us in this study.

COMMENT

It is obvious that the pathologic changes in the liver are very minimal in our patients. We are led to conclude that the functional capacity of the liver in thyrotoxicosis, as demonstrated by the tests employed by us, is hardly affected at all or is affected only to a very slight extent and that the pathologic changes in the liver in this condition are anything but striking, with the exception above noted of the nuclear vacuolization. At least it would appear that the anatomic changes otherwise must be so slight and so few that they elude demonstration by aspiration biopsy. It is conceded that this series is comparatively small. In addition, it may be argued that the negative findings on aspiration biopsy are inconclusive and that surgical excision biopsy may possibly demonstrate a different picture. However, it must also be remembered that the previous investigators reporting striking changes in

31. Ehrlich, P.: Ztschr. klin. med. **6**:33, 1883.

32. Warren, S.: The Pathology of Diabetes Mellitus, Ed. 2, Philadelphia, Lea & Febiger, 1938.

33. Chipps, H. D., and Duff, G. L.: Glycogen Infiltration of the Liver Cell Nuclei, Am. J. Path. **18**:645, 1942.

34. Popper, H.: Significance of Agonal Changes in the Human Liver, Arch. Path. **46**:132, 1948.

35. Popper, H., and Franklin, M.: Diagnosis of Hepatitis by Histologic and Functional Laboratory Methods, J. A. M. A. **137**:230, 1948.

36. Klatskin, G., and Yesner, R.: Hepatic Manifestations of Sarcoidosis and Other Granulomatous Diseases, Yale J. Biol. & Med. **23**:207, 1950.

37. Yesner, R., and Kunkel, P.: Preliminary Observations on the Effect of Aureomycin, Terramycin, Tibione, Combined Tibione and Streptomycin, and Chloromycetin on the Morphology of the Liver in Man, Yale J. Biol. & Med. **23**:299, 1951.

the liver of patients with thyrotoxicosis have remarked that the abnormalities were to be found particularly in the periphery of the liver—that is, in the very zone from which material is usually obtained by aspiration biopsy.

In a similar study recently carried out in Denmark by Piper and Poulsen,[28] comprising a series of 15 patients, the pathologic findings on the material obtained by liver aspiration biopsy were similar to ours in that no remarkable changes were actually observed. Of the 15 patients so studied, glycogen content was slightly reduced in two. Slight steatosis was found in three patients and slight round cell infiltration in two. Hyalinized connective tissue was found in one. The authors concluded that the changes were "few and slight, not at all suggestive of any characteristic pathological-anatomical picture; and, as mentioned, this is not because the cases here examined have been particularly mild or of short duration." (The basal metabolic rates in these patients ranged from +114 to +193.) The nuclear changes described by us were not found in the patients of Piper and Poulsen.

We are tempted to conclude that the discrepancy between the findings of previous authors, describing marked anatomical changes in the liver of patients with thyrotoxicosis, and the results of our own study, as well as that of Piper and Poulsen, is due to the fact that the previous authors drew their conclusions on the basis of autopsy material exclusively. Thus their observations were limited to those patients who were ill enough to die, either from a severe hyperthyroid state per se or, most likely, from such complications as infection and, particularly, operation or even from entirely unrelated conditions. It seems thus that patients with uncomplicated thyrotoxicosis are not to be expected to present any significant pathologic changes in the liver.

SUMMARY

Numerous reports in the literature on the subject of abnormal hepatic function and pathologic changes in the liver of patients with thyrotoxicosis are briefly reviewed. It is noted that there is prevalent a notion that the liver is frequently involved in thyrotoxicosis both functionally and structurally. It is pointed out that the knowledge of liver pathology in this condition is based on autopsy material and therefore deals with patients who were ill enough to die from hyperthyroidism or, more likely, from complications. Moreover, in these reports the clinical data are inadequate for evaluation of the role of complicating conditions or of some entirely unrelated factors which may damage the liver.

The present study was undertaken for the purpose of investigating the status of the liver, functional and anatomic, in living patients with thyrotoxicosis. A series of 13 patients were thus studied by performing liver aspiration biopsies and correlating anatomical material thus obtained with the results of a battery of hepatic function tests.

As a result of this study we are led to conclude that the functional capacity of the liver in thyrotoxicosis, as demonstrated by the tests employed by us, is hardly affected at all or is affected only to a very slight extent and that pathologic changes in the liver in this condition are anything but striking, with the exception of the vacuolization of the liver cell nuclei. The possible significance of nuclear vacuolization, or ballooning, is briefly discussed. The possible reasons for the discrepancy between the findings of previous investigators and our own are mentioned. It seems that patients with uncomplicated thyrotoxicosis are not to be expected to present any significant pathologic changes in the liver.

CLINICAL STUDIES IN GERIATRICS

I. Serum Lipid Partitions

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EXISTING knowledge concerned with the change of cellular metabolism associated with aging is limited. Available information on the relation of lipid metabolism to the aging process is also limited and has been the basis for considerable theoretical speculation. It has however latterly become understood that physiologic aging has no real relationship with such degenerative changes as atherosclerosis, which are associated with abnormalities of lipid metabolism. The hard calcified arteries of old age may show little if any of the focal intimal lesions termed atheroma, while the early fatty flecks of these lesions can be found in the soft flexible arteries of youth. Atheromata are selectively localized accumulations of cholesterol, cholesterol esters, and other lipid deposits in the arterial intima, causing intimal fibrous thickening. Atherosclerosis is primarily a disease of the intimal coat, and the important clinical consequence is interference with blood flow to essential organs. This is to be differentiated from generalized medial arteriosclerosis, which is associated with rigid calcified arteries but has no localized intimal accumulations interfering with blood supply. Changes in the medial coat resulting in atrophy, and even in necrosis, and calcification may occur with or without intimal lesions.[1]

Extensive statistical investigations by Keys and his associates [2] have indicated considerable variability in serum cholesterol levels correlated with age in various countries, dependent on percentage of fat in the daily diet. In countries in which large amounts of fat are included in the diet a constant increment in serum cholesterol levels was demonstrated from youth to aging years. In countries in which the diet is low in fat this increment continued only until 30 years of age and then serum cholesterol levels remained constant. In the latter countries the incidence of diseases associated with extensive atheromatosis is considerably lower.

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This study was aided by a grant from the Sophie G. Cohen and William W. Cohen Foundation.

1. Pathologic Physiology: Mechanisms of Disease, edited by W. A. Sodeman, Philadelphia, W. B. Saunders Company, 1950.

2. Keys, A.; Fidanza, F.; Scardi, V., and Bergani, G.: The Trend of Serum-Cholesterol Levels with Age, Lancet **2**:209 (Aug. 2) 1952.

We have been for some time interested in the clinical and biochemical aspects of atherosclerosis.[3] One of us,[4] investigating the relationship of age to serum cholesterol and phospholipid levels in residents of the United States, demonstrated a rise in these values until the seventh decade and then a leveling off and even a fall after age 70.

The present investigation was concerned with lipid partition studies in subjects over 80 years of age, in the hope that such a study might contribute some further information relative to lipid metabolism, atherosclerosis, and longevity.

MATERIALS AND METHODS

The study was conducted in a chronic disease hospital.[5] Blood was drawn for lipid studies from 26 male patients varying in age from 80 to 101 years. Serum partition evaluations which were done included determination of total lipids, total cholesterol, cholesterol esters, and phospholipids. In addition, colloidal red[6] determinations were done on each of the sera. In none of these subjects was there clinical evidence of malnutrition. There was no evidence of myocardial failure. In those subjects studied by x-ray there were marked calcifications of all the larger and medium-sized arteries. Autopsy records of this age group which are presently being studied for future publications show surprisingly minimal coronary atherosclerosis.

RESULTS

An unusually large number of these old people showed unusually low serum cholesterol levels. It can be seen from the Table that 18 of the 26 serum cholesterol determinations were lower than 200 mg. per 100 cc. Five of these sera showed cholesterol levels of less than 150 mg. per 100 cc. It is also interesting to note that in most instances the phospholipid/cholesterol ratio was one that is not considered to be associated with atherosclerosis. Only eight cholesterol determinations were over 200 mg. per 100 cc., and of these only two rose to levels that are ordinarily considered a slightly abnormal elevation.

The average serum cholesterol level was 188±80 mg. per 100 cc. This may certainly be considered to be at the lower limits of normal.

A relatively large number of these aged men showed positive serum colloidal red tests. This indicates the presence of abnormal serum colloids, probably a

3. Goldbloom, A. A.: Clinical Studies of Blood Lipid Metabolism: I. Normal Blood Lipid Variations of Phospholipids, Neutral Fats, Total Lipids, and Lipid Fraction Percentages, Am. J. Digest. Dis. **19**:9 (Jan.) 1952; III. Serial Serum Lipid Partitions in a Patient with Myocardial Infarction During the Acute, Recurrent, and Chronic Stages, Bull. New York M. Coll. **14**:75, 1952; VI. Serial Serum Lipid Partitions in Patients with Chronic Coronary Artery Disease, Am. Pract. & Digest. Treat. **3**:799 (Oct.) 1952; VII. Serial Serum Lipid Partitions During the 1st and 6th Week Periods in Patients with Acute Myocardial Infarction, to be published. Pomeranze, J., and Kunkel, H. G.: Serum Lipids in Diabetes Mellitus, Proc. Am. Diabetes A. **10**:217, 1950. Pomeranze, J., and Bienfield, W. H.: Fat Tolerance Relationship to Atherosclerosis, Bull. New York M. Coll. **14**:70, 1952. Pomeranze, J.; Greene, M. B., and Goldbloom, A. A.: Effect on Serum Lipids of Weight Reduction Without Marked Fat Restriction; Rigid Fat Restriction Without Weight Reduction, Bull. New York Acad. Med. **28**:611 (Sept.) 1952.

4. Pomeranze, J.: Medicinal Chemistry Section, Gordon Research Conference, Colby Junior College, New London, New Hampshire, August 1951.

5. The Bird S. Coler Hospital, Welfare Island.

6. Pomeranze, J.: Turbidimetric Studies of Serum Colloids in Diabetes Mellitus, Gastroenterology **17**:226 (Feb.) 1951.

reflection of hepatic dysfunction. The significance of this finding is not yet clear and will be correlated with other liver function studies in this age group.[7]

The incidence of hypertension was minimal. There appeared to be no correlations between blood pressure, weight, and serum lipids.

COMMENT

Ordinary senile arteriosclerosis which involves the media of larger and medium-sized arteries does not cause hypertension, nor is hypertension involved in its etiology. On the other hand, Evans has shown experimentally that continued pulsation of serum with abnormal lipids against normal intima at high pressures causes

Results of Lipid Studies in Twenty-Six Men Aged 80 to 101 Years

Patient	Blood Pressure	Weight, Lb.	Colloidal Red Test	Cholesterol	Cholesterol Esters	Phospholipids	Total Lipids
W. B.	120/50	123	4+	116	82	136	410
T. C.	105/50	120¾	0	134	78	140	515
B. G.	115/74	195	3+	137	82	148	504
C. G.	104/64	101	3+	137	80	152	494
F. W.	146/60	148	0	164	102	179	526
C. B.	86/60	113½	0	165	98	148	501
T. D.	100/50	88	2+	147	96	170	559
W. D.	110/70	183	2+	171	116	168	557
J. E.	160/90	80¾	1+	162	112	157	623
J. L.	110/60	143½	0	177	112	192	521
A. P.	130/60	136	2+	185	120	234	621
A. M.	150/80	129	2+	178	108	190	595
C. R.	134/70	188	4+	189	124	206	521
N. Q.	110/60	158½	4+	190	130	224	721
A. C.	150/90	151	2+	191	116	196	534
I. R.	120/60	85½	2+	195	120	184	647
G. D.	135/80	120	3+	198	118	190	692
G. M.	110/70	120	2+	184	122	201	619
B. Z.	130/70	111	2+	205	116	188	674
T. T.	115/60	100	1+	214	122	226	674
T. L.	150/80	161	0	222	120	207	647
R. M.	124/70	161	3+	225	112	194	651
F. K.	134/69	121½	3+	246	158	269	706
J. I.	100/70	120	4+	223	174	207	672
F. P.	160/90	163¾	4+	270	182	260	694
A. B.	120/70	184½	4+	274	166	280	671

intimal lipid infiltration analogous to localized atheroma.[8] Clinically, it is frequently observed that atheromatous patches are present at points of pressure in the vessel wall. When hypertension is present in the lesser circulation, atheroma appears. This is not found when tension in the lesser circulation remains at its normal level. The subjects observed in this study show marked x-ray and clinical evidence of generalized thickening and calcification of the media. In most of these subjects the blood pressure is at the lower levels of normal. Pathologic evidence of coronary atheroma is usually not present in these elderly persons, although the arterial tree may be rigid with medial calcifications.

7. Pomeranze, J.: The Effect of Diet and Therapeutic Agents on Serum Lipid Tolerance in Relationship to Atherosclerosis, J. Gerontol. (Supp. to No. 3) **6**:135 (Sept.) 1951.

8. Evans, S. M.; Ihrig, H. K.; Means, J. A.; Zeit, W., and Haushalter, E. R.: Atherosclerosis: An in Vitro Study of the Pathogenesis of Atherosclerosis, Am. J. Clin. Path. **22**:354 (April) 1952.

It is interesting to note the age-conditioned regression of atherosclerosis in the experimental animal.[9]

One might be led to infer from the levels obtained in this series that these persons lived this long because their lipid metabolism was adequate throughout life and able to handle the American high-fat diet. An ability to metabolize recurrent lipemia sufficiently well to prevent cholesterol deposition in the intimal wall as a foreign body may be inferred to be part of their constitutional endowment.

One might also infer that when a person has successfully passed a certain crucial age level, regression of atheromata takes place and serum lipid abnormalities become less evident.

The answer can only be determined by repeated serum cholesterol determinations in the same individuals over a large span of their existence.

CONCLUSIONS

1. Serum lipids in 26 men aged 80 to 101 years were found to be at surprisingly low levels.

2. These low serum lipid levels were not related to wasting in the subjects observed.

3. The serum lipid values were independent of weight, cardiovascular abnormalities, and blood pressure.

4. Generalized arteriosclerosis as evidenced by medial necrosis and calcification is to be differentiated from atheromatosis, which is apparently related to abnormal lipid metabolism.

5. A high incidence of positive colloidal red tests was found, the significance of which is not yet clear.

9. Pick, R.; Stamler, J.; Rodbard, S., and Katz, L. N.: The Inhibition of Coronary Atherosclerosis by Estrogens in Cholestrol-Fed Chicks, Circulation **6**:276 (Aug.) 1952.

IDIOPATHIC ULCERATIVE COLITIS

Giant Ulceration Following Corticotropin (ACTH) and Cortisone Therapy

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THE USE of corticotropin (ACTH) for patients with severe ulcerative colitis usually is accompanied by striking subjective improvement. Objective evidence of healing, however, has not been noted as frequently, and adverse effects including activation of peptic ulcers and perforation of the colon have been reported.[1]

This report is based upon observations made on 14 patients having severe or fulminating ulcerative colitis who were treated with intravenous corticotropin at Duke Hospital and on one other patient who was treated elsewhere. Five of these patients subsequently were operated upon, four having a colectomy and the fifth an ileostomy only. Large atypical undermined ulcers were present throughout the colon and rectum in the four patients in whom colectomy was done.

CLINICAL MATERIAL AND METHODS

The clinical data on the 15 patients who received corticoid therapy are shown in the Table. The clinical course of the disease prior to treatment was classified as fulminating in 11 of these patients and as severe in the remaining 4. Roentgen examination of the colon demonstrated universal involvement in eight patients, right-sided colitis which subsequently spread to the left in three, and left-sided colitis in the remaining four.

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Dr. David Klein, Wilson Laboratories, Chicago, provided corticotropin and corticotropin gel and Dr. Elmer Alpert, Merck & Company, Rahway, N. J., provided the cortisone (Cortone) acetate used in the treatment of certain of the patients, which was made available through Dr. F. L. Engle, Duke Hospital.

1. Machella, T. E.: Problems in Ulcerative Colitis, Am. J. Med. **13**:760 (Dec.) 1952. Sloan, S.; Briggs, J. D., and Halstead, J. A.: ACTH Therapy for Ulcerative Colitis Complicated by Perforation of Coexisting Peptic Ulcer, Gastroenterology **18**:438 (July) 1951. Tulin, M.; Kern, F., Jr., and Almy, T. P.: Perforation of the Bowel During Treatment of Ulcerative Colitis with Corticotropin: Report of 3 Cases, J. A. M. A. **150**:559 (Oct. 11) 1952.

Clinical Data on Fifteen Patients with Ulcerative Colitis Treated with Corticotropin and Cortisone

Case	Age	Sex	Duration of Disease	Severity on Admission	Clinical Course	X-Ray Involvement	ACTH* or Cortisone: Daily Dose, Units	ACTH* or Cortisone: Days, No.	Follow-Up Period, Mo.	Response to ACTH and Cortisone
1	42	F	6 yr.	Severe	Ful.*	Universal	80 I. M.* 20 I. V.* 20 I. V. (Cortisone)	9 4 10	21	Subjective and proctoscopic improvement, slight x-ray improvement; mild symptoms at present
2	43	M	18 yr.	Severe	Ful.	Universal	80 I. M. 20 I. V. 20 I. V.	5 6 12	19	Developed x-ray signs of perforation on 5th day of I. M. ACTH; temperature rose, but no definite signs of peritonitis; moderate recovery with conservative management, including proctoscopic improvement, but x-ray shows progression of disease
3	32	F	1 yr.	Severe	Ful.	Universal	20 I. V.	8	18	Temporary clinical improvement, but no change in proctoscopic or x-ray appearance; ileostomy 3 days after ACTH stopped; asymptomatic at present
4	18	F	18 mo.	Severe	Ful.	Right to left spread	20 I. V.	17	18	Clinical and proctoscopic recovery; x-ray improvement; asymptomatic at present
5	42	F	7 wk.	Severe	Ful.	Universal	20 I. V. 20 I. V.	8 10	15	Striking clinical improvement, but subsequent relapse with development of coalescing undermined ulcers; colectomy; clinical recovery
6	14	F	2 mo.	Severe	Ful.	Universal	40 gel* I. M. 80 gel I. M. 20 I. V.	8 8 14	12	Clinical remission with marked x-ray improvement following I. V. ACTH; undermined ulcers developed following ACTH; clinical remission since treatment
7	20	F	1 mo.	Severe	Ful.	Right to left spread	20 I. V. 20 I. V.	13 15	12	Temporary clinical remission after each course; x-rays showed spread of disease; mild symptoms at present
8	22	F	6 wk.	Severe	Ful.	Universal	20 I. V. 20 I. V. 20 I. V.	12 12 8	10	Temporary clinical remission after each course, but became more severe, with development of undermined ulcers; colectomy; clinical recovery
9	27	F	1 yr.	Moderate	Severe	Left sided	20 I. V. 80 I. M.	7 1	9	Clinical and proctoscopic improvement; no change in x-rays
10	39	M	1 yr.	Moderate	Severe	Left sided	20 I. V.	9	9	Clinical, proctoscopic, and x-ray improvement; x-rays became worse with relapse 4 mo. after ACTH; asymptomatic at present
11	18	F	9 mo.	Severe	Ful.	Universal	20 I. V. 60 I. M.	11 12	9	Slight temporary clinical improvement; development of coalescing punched-out ulcers while on I. M. ACTH; colectomy; recovery
12	45	F	6 yr.	Moderate	Severe	Left sided	20 I. V.	11	8	Clinical and proctoscopic improvement; no change in x-rays; mild symptoms at present
13	28	M	8 yr.	Moderate	Severe	Left sided	20 I. V.	11	7	Marked clinical and proctoscopic improvement; no change in x-rays
14	25	F	8 yr.	Severe	Ful.	Universal	20 I. V.	10	4	Clinical and proctoscopic recovery; no change in x-rays
15	69	F	9 mo.	Severe	Ful.	Right to left spread	Cortisone & ACTH	..	7	Treated with cortisone and ACTH elsewhere; disease spread, with development of giant ulcers; colectomy; recovery

* The abbreviations are as follows: ACTH, corticotropin; Ful., fulminating; I. M., given intramuscularly; I. V., given intravenously; gel, corticotropin gel.

Fourteen patients received daily intravenous infusions of 20 units of corticotropin for approximately 12-hour periods from 4 to 17 days (mean 10.3 days).[2] Twenty courses of intravenously administered corticotropin were given to the 14 patients. Three patients also received courses of corticotropin intramuscularly (80 units per day) for periods of 5 to 13 days (mean 10 days), and one patient was treated with corticotropin gel (40 to 80 mg. per day) for a 16-day period prior to intravenous therapy. Cortisone was taken by four patients in this series, either before or after the course of corticotropin. Antibiotics were administered concurrently.

RESULTS OF TREATMENT WITH CORTICOTROPIN

Dramatic clinical improvement was observed within 24 to 48 hours in 13 of the 14 patients receiving corticotropin intravenously. Diarrhea and bleeding decreased, and the stools became more normal in consistency. Erythema nodosum and arthralgia, present in three patients, subsided rapidly. Improvement in the sigmoidoscopic picture was noted in 11 of 12 patients having sigmoid involvement. This improvement consisted primarily in a decrease in the inflammatory reaction and was classified as slight in one patient, moderate in five, and marked in the remaining five patients. Large, coalescent, punched-out ulcers with undermined edges, usually considered typical of amebiasis, developed in four patients following the use of corticotropin intravenously and in one patient who had received cortisone and intramuscularly administered corticotropin. The mucosa between these ulcers was essentially normal.

Improvement in the appearance of the colon as seen by x-ray examination was noted in 8 of the 15 patients. The x-ray appearance was unchanged in five and worse in the remaining two patients. This improvement was classified as slight in four, moderate in three, and marked in one patient. Decrease in edema was the most frequent roentgenological finding. In some patients the ulcers gradually decreased in size. Shortening of the colon was noted in three patients. Large crater-like ulcers were observed in four patients, two of whom initially had shown roentgen evidence of improvement. These cases are reported in detail.

REPORT OF CASES

Case 5.—J. M. T., A 43-year-old woman, entered Duke Hospital on Nov. 15, 1951, with a history of bloody diarrhea of seven weeks' duration. This was accompanied by chills, fever, and a 17-lb. (7.7 Kg.) weight loss. Corticotropin intramuscularly (80 mg. per day) had been given for six days without response four weeks prior to admission. Examination revealed a febrile (39.6 C.) dehydrated woman. Proctoscopic examination revealed a granular hemorrhagic mucosa with multiple small ulcerations. A flat x-ray of the abdomen showed a gas-filled colon with a thickened irregular mucosal pattern. Barium enema (Fig. 1*A*) revealed acute colitis of the entire colon. Corticotropin (20 units per day) was administered intravenously for eight days. Proctoscopic examination following this therapy showed marked improvement. There was some granularity but little evidence of inflammation. Clinical improvement persisted although the temperature again rose to 38 C. daily. Proctoscopic examination (Jan. 3, 1952) revealed a granular mucous membrane with scattered shallow ulcers. On examination two weeks later 14 cm. of the mucous membrane was entirely normal, but above this there were several large punched-out ulcers. By Jan. 31, 1952 the ulcers had enlarged and were noted to have undermined edges. During this period the patient's clinical course remained unchanged; there were two to five stools per day, with a low grade fever. Repeated proctoscopic examinations during the next six months showed the same punched-out ulcers. Barium enema (Fig. 1*B*) showed less evidence of acute disease

2. Gordon, E. S.; Kelsey, C., and Meyer, E. S.: Adrenal Stimulation by Intravenous ACTH, in Mote, J. R., Editor: Second Clinical ACTH Conference, New York, The Blakiston Company, 1951, Vol. 2, p. 30.

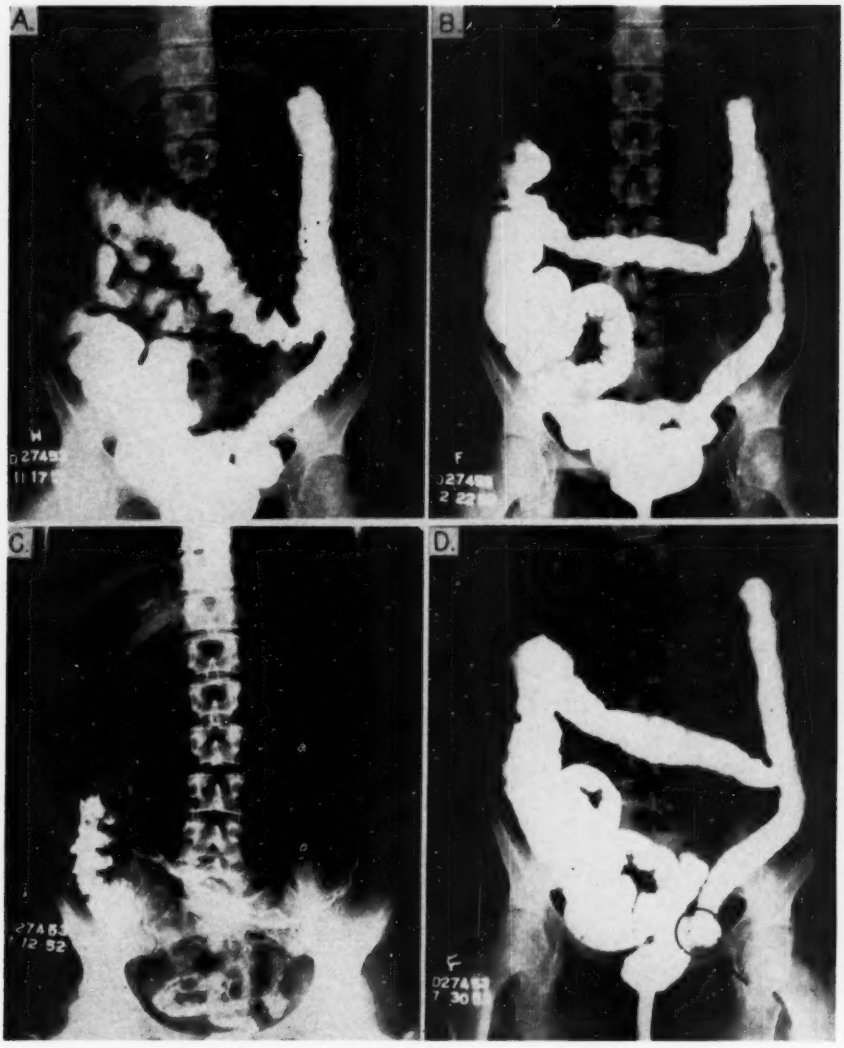

Fig. 1 (Case 5).—*A*, acute generalized colitis; *B*, initial improvement after corticotropin therapy; *C*, punched-out ulcers in rectum on postevacuation film; *D*, crater-like ulcers throughout colon, most marked in sigmoid and rectum, following corticotropin therapy.

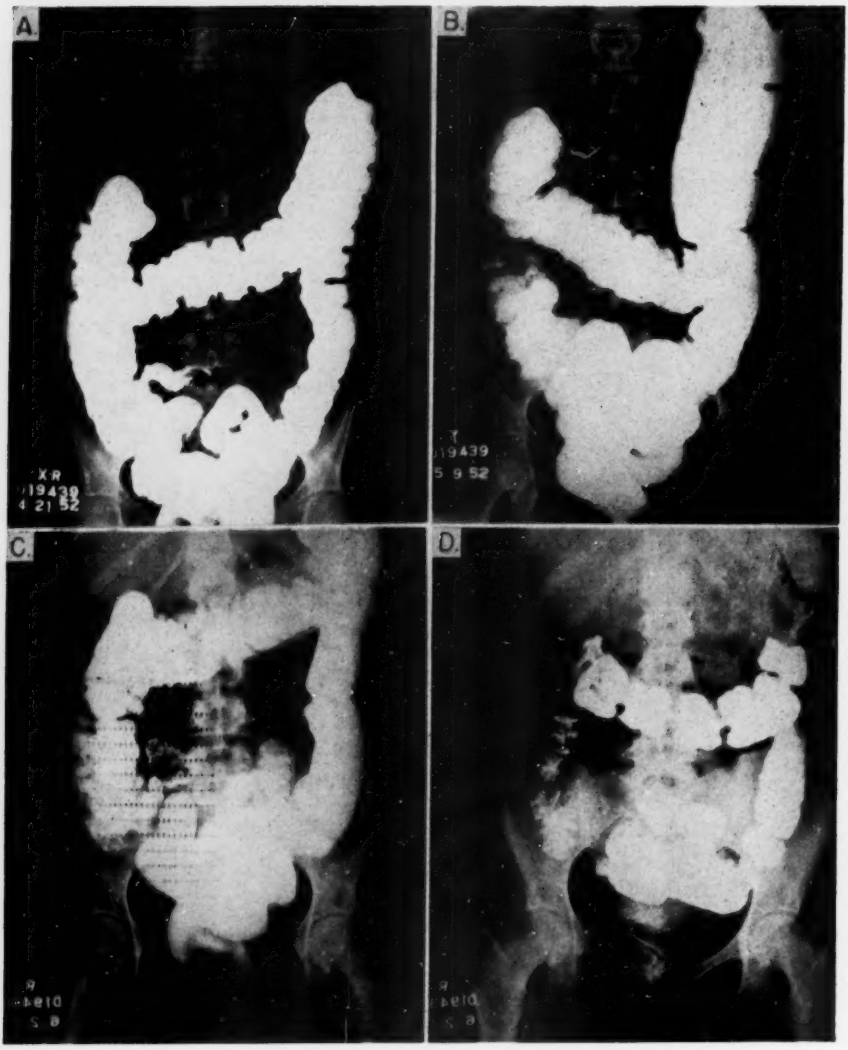

Fig. 2 (Case 8).—*A*, extensive colitis involving all but sigmoid; *B*, examination six weeks later showing little change; *C* and *D*, marked improvement following initial course of corticotropin.

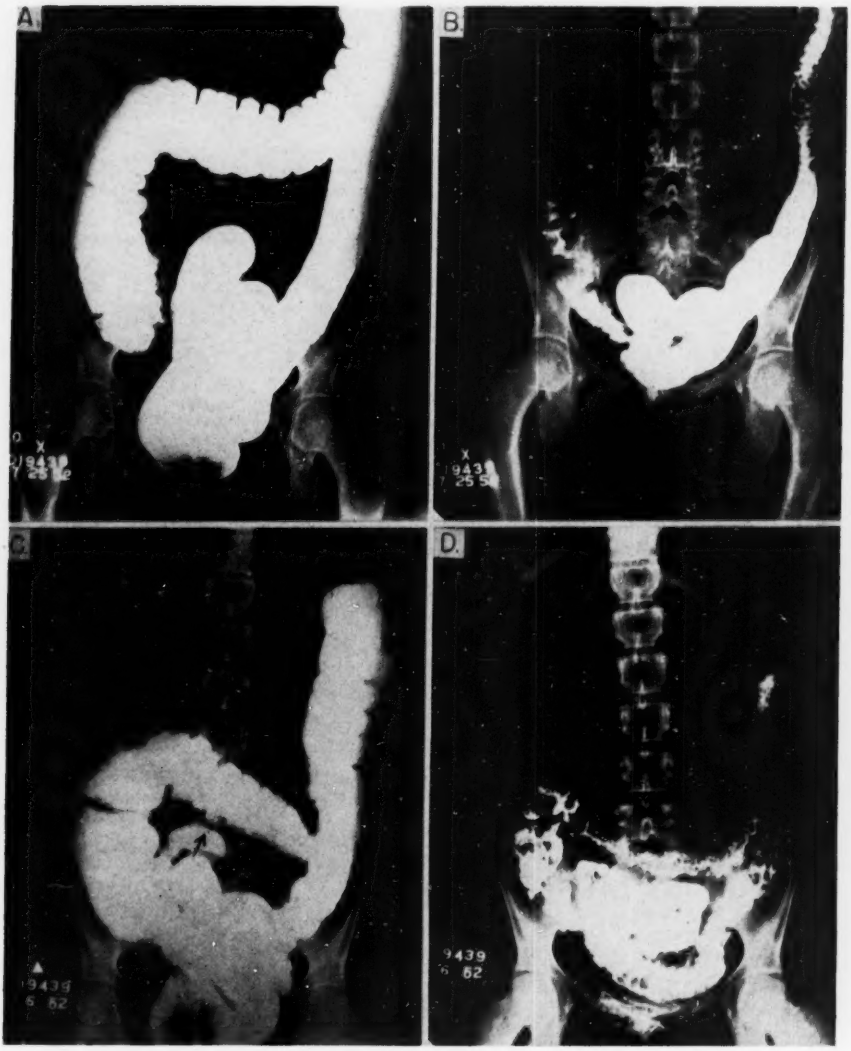

Fig. 3 (Case 8).—*A* and *B*, small ulcerations throughout colon following second course of corticotropin; *C* and *D*, large penetrating ulcer craters throughout colon after third course of corticotropin.

but more scarring with some shortening of the colon. A subsequent x-ray study (July 12, 1952; Fig. 1*C*) revealed large punched-out ulcers in the rectum, the remainder of the colon being unchanged.

The patient was readmitted to Duke Hospital (July 28, 1952) with a recurrence of diarrhea. Proctoscopic examination revealed no change. Barium enema (Fig. 1*D*) revealed extensive ulceration throughout the colon, being most marked in the rectum. The ulcers were larger but the inflammatory reaction was less than that noted on the first admission. Corticotropin was administered intravenously for 10 days, with some symptomatic improvement. Proctoscopy 10 days after completion of treatment showed a tendency toward healing of the large ulcers, but examination one month later again showed numerous shallow and deep ulcers with pseudopolyp formation. Colectomy was performed on Sept. 12, 1952.

The surgical specimen was 120 cm. in length. There were numerous small ulcers in the cecum and rectum and a longitudinal 2 by 5 cm. ulcer in the transverse colon. The mucosa was edematous and hemorrhagic and polypoid in the distal colon. These polypoid areas were due to a markedly edematous and hemorrhagic submucosa. The ulcers varied, some being simple

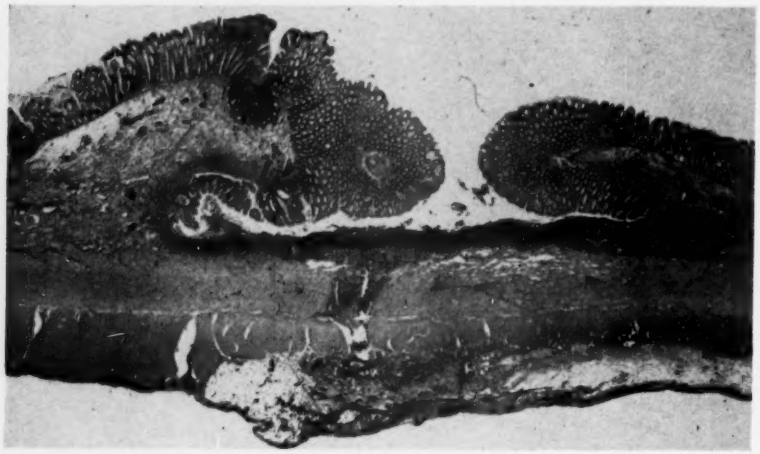

Fig. 4 (Case 8).—Cross section of a large longitudinal ulcer, showing pronounced overhanging edges, with an inflamed denuded submucosal floor and edema of the adjacent submucosa and subserosa. There are pinpoint mucosal ulcers just to the left of the large ulcer.

erosions with polymorphonuclear infiltrates in the submucosa, others showing submucosal hemorrhage or congestion, granulation tissue, and large focal collections of lymphocytes. There were overhanging mucosal margins. The intervening mucosa was also greatly altered, showing focal thinning, early mucosal crypt-like ulcers, congestion, edema, and moderate cystic dilatation of some glands.

Case 8.—C. Z., a 22-year-old woman, was admitted on April 26, 1952 complaining of a bloody diarrhea of six weeks' duration, chills, fever, and erythema nodosum. Proctoscopic examination showed no abnormalities, but a barium enema (Fig. 2*A*) showed extensive colitis involving the entire colon with the exception of the sigmoid and rectum. Corticotropin was given intravenously for 12 days, followed by gradually decreasing doses of oral cortisone. The patient had a prompt symptomatic remission. However, x-ray studies demonstrated involvement of the terminal ileum, and repeat barium enema (Fig. 2*B*) showed little change from the previous examination. Barium enema (Fig. 2 *C* and *D*) one month later showed marked improvement, but the patient soon had a recurrence of her colitis, accompanied by arthralgia, fever, and vomiting and was readmitted on June 12, 1952. Following daily intravenous administration of corticotropin for 12 days she had a prompt symptomatic remission. One month later proctoscopy showed no abnormalities, and the barium enema showed the presence of small ulcerations (3*A*

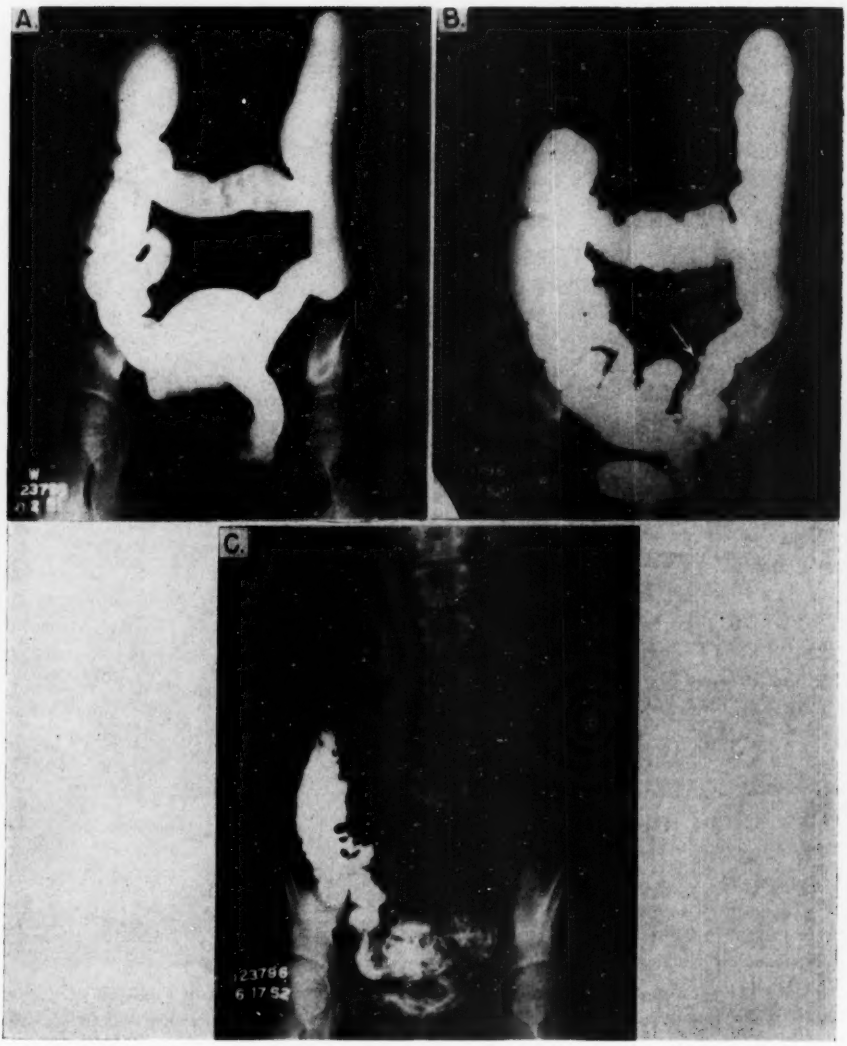

Fig. 5 (Case 11).—*A*, smooth serrated colon before therapy with corticotropin; *B* and *C*, numerous crater-like lesions after therapy with corticotropin.

and *B*). Despite the use of 50 to 75 mg. of cortisone per day there was a recurrence of the bloody diarrhea accompanied by arthralgia and weight loss. The patient was admitted for the third time on Nov. 3, 1952, with a severe recurrence again accompanied by erythema nodosum. Barium enema (Fig. 3*C* and *D*) demonstrated large penetrating ulcers throughout the colon. Corticotropin was given intravenously for six days with some symptomatic improvement. However, proctoscopic examination at this time revealed punched-out undermined ulcers in the sigmoid, with normal surrounding mucosa. Subtotal colectomy with removal of the terminal 12 in. (30 cm.) of ileum and ileosigmoidostomy was performed on Nov. 12, 1952.

The resected colon measured 80 cm. in length, with an additional 10 cm. of terminal ileum attached. Numerous longitudinal ulcers were found throughout the extent of the resected colon and were virtually identical with those described in the previous case (Fig. 4). The terminal ileum involvement was mostly confined to the mucosa although there was some submucosal edema. The mucosa was congested and edematous. Hemorrhages and inflammatory cell infiltrates

Fig. 6 (Case 11).—These two strips of colon are representative of this total colectomy specimen. Longitudinal ulcers are visible in the central portion of the upper segment and at the left on the lower segment of colon. Virtually all of the remaining mucosa is abnormal, showing a pseudopolypoid shaggy appearance due to edema, and numerous pinpoint ulcers.

were present in the stroma between glands, and small focal mucosal ulcers surrounded by polymorphonuclear reaction were seen.

Case 11.—D. McL., an 18-year-old girl, was seen on Oct. 1, 1951, with a history of bloody diarrhea for four weeks. Proctoscopy revealed acute ulcerative colitis which appeared to be limited to the rectum. Barium enema (Fig. 5*A*) showed the colon to be smoother than normal, with some suggestion of serrations in the transverse colon. The patient was hospitalized (May 7, 1952) because of severe bloody diarrhea, chills, fever, and weight loss. Proctoscopic examination revealed an acutely inflamed granular mucosa. Corticotropin was administered intravenously for 10 days, with subsequent decrease in fever but little change in the diarrhea. Proctoscopic examination three days after completion of therapy showed slight improvement. Corticotropin (60 units per day) was administered intramuscularly from June 14 to June 25, 1952. Except for some decrease in the temperature, there was no change in other symptoms following the

intramuscular use of corticotropin. Barium enema at this time demonstrated severe universal involvement including the terminal ileum, with numerous large ulcerations (Fig. 5 *B* and *C*). Numerous punched-out ulcers with undermined edges were noted also at proctoscopy. Colectomy was performed on July 2, 1952.

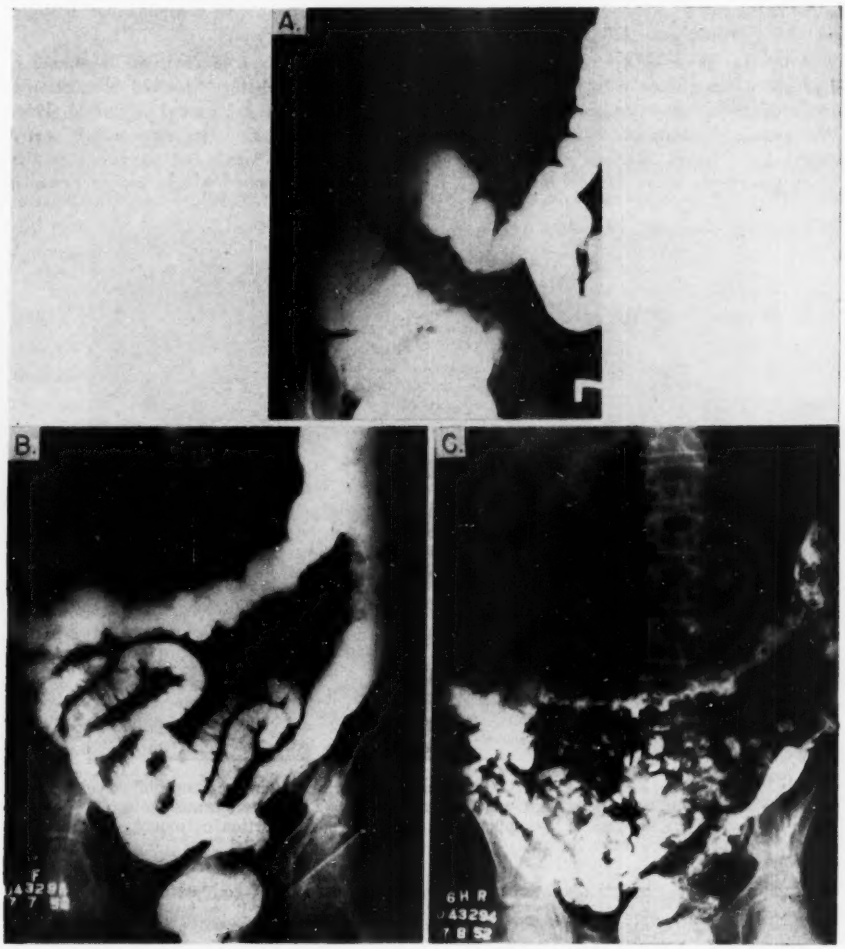

Fig. 7 (Case 15).—*A*, filling defect in hepatic colon, remaining colon normal; *B* and *C*, large crater-like lesions throughout colon following corticotropin therapy.

The surgically removed colon was 120 cm. in length. Longitudinal ulcers were present throughout the entire colon, except for a 20 cm. segment of transverse colon and 8 cm. segment of descending colon which were essentially normal (Fig. 6). The submucosal floor of the ulcers was covered by fibrin and polymorphonuclear cells, granulation tissue, and lymphocytic and plasma cell infiltrations. Many small focal mucosal ulcers were seen. Congestion, edema, polypoid alteration, interruption of the muscularis mucosae, and some cystic alteration of the colon glands were observed.

CASE 15.—L. B., a 69-year-old woman, was hospitalized elsewhere, in November 1951, because of abdominal pain, diarrhea, and polyarthritis. A presumptive diagnosis of rheumatic fever was made, and she was treated with cortisone. Although her fever and arthritis responded to this, the diarhea and weight loss continued. Barium enema (Jan. 17, 1952) showed a filling defect in the hepatic colon (Fig. 7 *A*). The remainder of the colon was normal. A right hemicolectomy was performed. The surgical specimen showed a 3 cm. ulcer with overhanging edges in the colon and a similar lesion in the cecum. Histologic study showed a granulomatous ulcer containing several giant cells. Bacteriologic study gave negative results.

After the operation the patient continued to have symptoms, and proctoscopic examination disclosed a large ulcer with overhanging edges at 15 cm. The patient received corticotropin and antibiotic therapy without response. She was admitted to Duke Hospital on July 5, 1952. Proctoscopic examination again showed a large ulcer with overhanging edges which partly encircled the bowel. Barium enema demonstrated marked irregularity and ulceration of the lower descending colon (Fig. 7 *B* and *C*). Because of the continued weight loss, arthralgia,

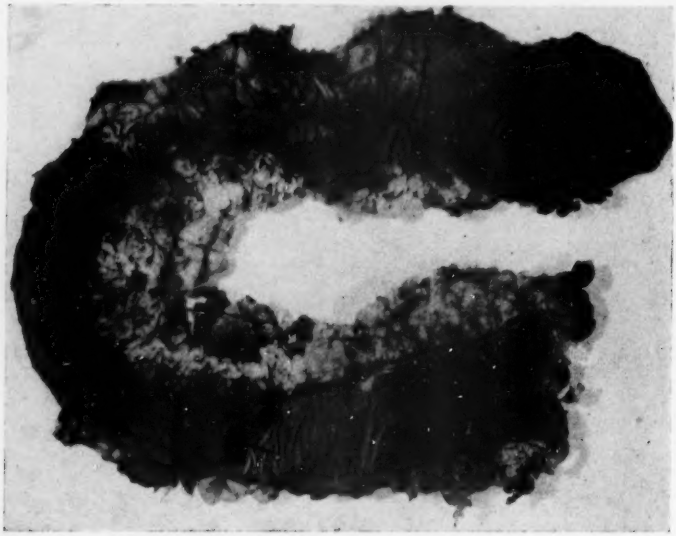

Fig. 8 (Case 15).—Partial colectomy specimen showing extensive longitudinal ulcer with surrounding edematous hemorrhagic mucosa on the left. The pseudomembranous floor of two large oval ulcers is present at the upper right. Only a small portion of mucosa in the lower middle part of the Figure is normal.

fever, and diarrhea, resection of the remaining colon was advised and performed on July 14, 1952.

The resected segment of colon measured 76 cm. in length and was again characterized by longitudinal ulcers measuring up to 10 cm. in length. These ulcers extended to the muscularis and were characterized by chronic inflammation, submucosal edema, and graulation tissue with little fibrosis. The mucosal margins of the ulcers were overhanging, with undermining of the mucosa by the inflammatory process, in some instances by as much as 1 cm. The mucosa between the ulcers was edematous and congested. Only a small segment of mucosa remained relatively normal (Fig. 8).

COMMENT

The usual sigmoidoscopic picture of ulcerative colitis consists of hyperemia, edema, and granularity. A diffusely involved granular, pitted, oozing mucosa with pinpoint to pinhead ulcerations is observed in more advanced stages, while in

fulminating cases the mucosa may be completely replaced by large ulcers. The punched-out ulcerations with relatively normal intervening mucosa observed proctoscopically in these cases of idiopathic ulcerative colitis following corticoid therapy resembled those seen in amebic colitis and were distinctly unusual in our experience.[3] Similar ulcers were found throughout the colon in the resected specimens. There was no evidence of amebiasis in the microscopic sections through these ulcers.

The roentgenographic changes seen in ulcerative colitis vary with the stage of the disease. In the fulminating type these consist of extreme edema with inflammatory reaction often involving the entire colon and the terminal ileum. Small ulcerations or a shaggy edematous mucosa with large ulcerations may be present. In the acute but nonfulminating case the roentgenographic picture ranges from mucosal edema without demonstrable ulceration to an ulcerative process associated with marked mucosal changes. These ulcerations are usually superficial, without deep crater formation. A narrowed tubular rigid colon is seen in the chronic case.

In the cases treated with corticotropin several variations from the usual roentgenologic picture have been observed. The most consistent of these was rapid subsidence of evidence of edema and inflammatory reaction. Rapid healing with complete disappearance of the ulcers was observed in some cases. The relapses following discontinuance of corticoid therapy were characterized by the development of giant bizarre ulcers with deep crater formation. The degree of accompanying edema and inflammatory reaction was significantly less than that usually seen at this stage. There was no constant correlation between the roentgenologic findings and the clinical course of the disease.

The pathologic changes in the colons of those patients subjected to colectomy after receiving corticoid therapy also were unusual. Longitudinal ulcers which penetrated to the submucosa and extended from a few centimeters to half the length of the colon were found in every case. They measured 1 to 2 cm. in width and had overhanging margins with undermining of the adjacent mucosa. The ulcers involved the mucosa away from the taenia more often than they involved the mucosa overlying the taenia.[4] The inflammatory responses observed microscopically also were similar in the four cases. The floor of the ulcers consisted of fibrin, polymorphonuclear exudate, and granulation tissue which was surrounded by zones of lymphocytic and plasma cell infiltration. These inflammatory changes involved the muscularis and serosa in some areas. The mucosa between the large ulcers appeared relatively normal in some places, while in others numerous pinpoint ulcers were observed. Fibrosis, conspicuous mucosal regeneration, healed ulcer beds, and foreign body type granulomas were absent. Marked shortening of the colon and other indications of long-existing severe disease were not observed despite the fact that the disease had been present for approximately a year in each of the four cases. The above-mentioned pathological changes, with the long undermined ulcers unaccompanied by significant fibrosis found in each of the cases following treatment with corticotropin and cortisone, are similar to those occasionally seen in fulminating

3. Bone, F. C.; Ruffin, J. M.; Baylin, G. J., and Cassel, C.: The Clinical Course of Idiopathic Ulcerative Colitis: Prognostic Implications, South. M. J. **43**:817 (Sept.) 1950.

4. Lium, R., and Porter, J. E.: Observations on the Etiology of Ulcerative Colitis: III. The Distribution of Lesion and Its Possible Significance, Am. J. Path. **15**:73 (Jan.) 1939. Warren, S., and Sommers, S. C.: Pathogenesis of Ulcerative Colitis, ibid. **25**:657 (July) 1949.

severe ulcerative colitis. They are unusual, however, because of their marked similarity and their development in severe form within a short period after use of corticotropin and cortisone was discontinued.

The deep undermined ulcers and absence of fibrosis may be related to the use of corticotropin and cortisone. Corticoid therapy suppresses inflammatory reaction [5] and retards the connective tissue component of wound healing.[6] The most striking effects of corticotropin and cortisone have been observed in the collagen diseases, in which prompt suppression of the clinical symptoms has followed their administration. It has been suggested that ulcerative colitis is a collagen disease, because of "a virtual absence of the homogeneous ground substance of the basement membrane of the epithelial cells."[7] It may be that these punched-out ulcers represent a rebound phenomenon after the corticoid therapy has been discontinued, such as has been observed in the collagen diseases.

On the other hand, it is possible that these undermined ulcers are caused directly by corticoid therapy. Brown [8] has observed the development of ragged atypical ulcers in previously normal colons in two patients with rheumatoid arthritis who had been treated with cortisone. Halstead and co-workers [9] also noted similar ulcers in the ileum following corticotropin therapy in a patient with ulcerative colitis.

The administration of corticotropin, especially by the intravenous route, appears to be life saving in some instances.[10] It is possible that the fulminating cases in this series would have terminated fatally had corticotropin therapy not been used. Lahey [11] indicated that because of the ability of corticotropin to induce a clinical remission, it is no longer necessary to perform ileostomy and colectomy in the acute stages of ulcerative colitis, in which the mortality is high. However, it is apparent that its use in this disease is not without danger.

SUMMARY AND CONCLUSIONS

Fifteen patients with severe or fulminating ulcerative colitis were treated with corticotropin (ACTH) or cortisone, 14 receiving corticotropin intravenously. Eight patients had sustained improvement, while the remaining seven either had only temporary improvement or became worse.

Perforation of the colon developed in one patient, and large undermined ulcers developed in four patients who subsequently had a colectomy. The colectomy specimens showed longitudinal undermined ulcers unaccompanied by significant fibrosis or mucosal regeneration.

5. Gruber, R.: Therapeutic Suppression of Tissue Reactivity: I. Comparison of the Effects of Cortisone and Aminopterin, Am. J. M. Sc. **221**:169 (Feb.) 1951.

6. Creditor, M. C.; Bevans, M.; Mundy, W. L., and Ragan, C.: Effect of ACTH on Wound Healing in Humans, Proc. Soc. Exper. Biol. & Med. **74**:245 (May) 1950.

7. Levine, M. D.; Kirsner, J. B., and Klotz, A. P.: A New Concept of the Pathogenesis of Ulcerative Colitis, Science **114**:552 (Nov. 23) 1951.

8. Brown, P. W., in discussion on Sauer, W. G.; Brown, P. W., and Dearing, W. H.: Corticotropin in Regional Enteritis, Gastroenterology **22**:563 (Dec.) 1952.

9. Halstead, J. A.; Adams, W. S.; Sloan, S.; Walter, R. C., and Bassett, S. H.: Clinical Effects of ACTH in Ulcerative Colitis, Gastroenterology **19**:698 (Dec.) 1951.

10. Kirsner, J. B., and Palmer, W. D.: ACTH in Ulcerative Colitis—Report of Progress, Gastroenterology **18**:143 (May) 1951.

11. Lahey, F. H.: Indications for Surgical Intervention in Ulcerative Colitis, Ann. Surg. **133**:726 (May) 1951.

The sigmoidoscopic appearance of these ulcers and the accompanying roentgenologic changes were distinctly different from what is usually seen in cases of idiopathic ulcerative colitis in which corticoid therapy is not given.

Corticotropin and cortisone appear to alter the course of idiopathic ulcerative colitis.

ADDENDUM

Since submission of this paper we have followed an additional patient, who was observed to have huge linear ulcers, one of which perforated, transecting the entire length of the transverse colon, following intravenous therapy with corticotropin.

A brief report of this case together with the autopsy findings follows.

CASE 16.—M. H. R., a 62-year-old woman, entered Duke Hospital on Jan. 26, 1953, with bloody diarrhea, chills, and fever. She had a past history of intermittent rectal bleeding for the past three and one-half years. Physical examination revealed an obese white female, weighing 152 lb. (68.4 kg.). Proctoscopic examination showed a narrow lumen which was granular and hemorrhagic. Barium enema demonstrated a narrowed serrated colon. During the first week in the hospital the temperature rose to 38.4 C. daily and the patient had 10 to 12 bloody stools per day. Corticotropin (20 units per day) was given intravenously for six days. During this period the patient's temperature decreased, and her stools improved. Following cessation of corticotropin therapy, however, she again had 10 to 15 stools per day. She refused all medication and diagnostic studies, directing treatment herself and restricting her food intake to liquids. She was seen in consultation by the psychiatrist who noted that she was depressed but rational. Surgery was recommended, but the patient steadfastly refused. During the succeeding month she had a normal or subnormal temperature with a rapid pulse. She continued to have frequent liquid bloody stools, and her weight decreased to 130 lb. (58.5 kg.). Necrotic changes developed in the skin beneath both breasts.

On March 4, 1953, her abdomen was noted to be protuberant, tympanitic, and tender. She was afebrile, but her pulse was elevated. Flat x-ray of the abdomen (March 5, 1953) showed enormously distended loops of small bowel with a large collection of gas in the midabdomen. The white blood cell count was 34,000. It was thought that the patient had a perforation of the colon with a walled-off abscess, but surgery was again refused. On March 7, 1953, a necrotic spot in the center of the umbilicus was opened with a clamp which entered a large abscess cavity containing gas and feces. The patient continued to have bowel movements, and normal bowel sounds were present. However, her temperature began to rise, and on March 13, 1953, excision of the necrotic skin beneath the breasts and drainage of the abscesses in the abdomen were performed. The patient died on March 14, 1953.

At autopsy the anterior abdominal wall was adherent to a large open segment of the transverse colon, 27 cm. in length and 5 cm. in width. The anterior wall of the transverse colon appeared to be completely dissolved away by the ulcerative process. There was also a localized abscess associated with perforation of the cecum and ascending colon. The remaining colon showed huge, deep, linear ulcers, which were surrounded by considerable mononuclear inflammatory response. Although some mucosal regeneration was observed, again there was virtually no fibrous reaction.

DIAGNOSTIC IMPORTANCE OF CAFÉ-AU-LAIT SPOT IN NEUROFIBROMATOSIS

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IN CUTANEOUS medicine, von Recklinghausen's neurofibromatosis is recognized as a complex of macular pigmented areas and tumors, either cutaneous or subcutaneous, often accompanied by a number of polymorphous peripheral and central abnormalities. The initial descriptions of the physical and pathological findings in this disease, as given by Rayer,[1] Smith,[2] and von Recklinghausen,[3] did not include the pigmentary changes. The addition of these changes to the primary complex may be credited to Marie and Bernard [4] and to Chauffard.[5] The macular pigmented areas associated with neurofibromatosis are melanic in origin, are located in and around the basal cell layer of the epidermis, and are commonly called café-au-lait spots, because of their characteristic color—that of coffee with milk. Café-au-lait spots may vary in size and configuration, may be single or multiple, and may be located on any part of the body. However, in contrast to the ephelides, they are more prevalent in the unexposed areas of the skin. Café-au-lait spots, while generally present soon after birth, may develop during the first or second decade. There are no symptoms referable to the café-au-lait spot per se, and, in contrast to the lentigo, it is not known to undergo malignant degeneration. Neither the frequency of the café-au-lait pigmentation in the general population nor the extent to which these spots are concomitant with the diagnosis of neurofibromatosis has been adequately explored. Furthermore, the correlation in

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1. Rayer, cited by Grön, K.: "Forme Fruste" of v. Recklinghausen's Disease (Neurofibromatosis Disseminata Multiplex), Brit. J. Dermat. **35**:364, 1923.

2. Smith, R. W.: A Treatise on the Pathology, Diagnosis and Treatment of Neuroma, 1849; reprinted in whole as An Atlas of Illustrations of Pathology, London, New Sydenham Society, 1898, p. 38.

3. von Recklinghausen, F.: Über die multiplen Fibrome der Haut und ihre Bezeihung zu den multiplen Neuromen: Festschrift für Rudolf Virchow, Hirschwald, Berlin, 1882.

4. Marie, P., and Bernard, A.: Neurofibromatose généralisée, Soc. med. hôp., Paris **13**:200, 1896.

5. Chauffard, M. A.: Dermato-fibromatose pigmentaire (ou neuro-fibromatose généralisée), Soc. med. hôp., Paris **13**:777, 1896.

pigmentary changes between members of families in which neurofibromatosis is occurring has not been investigated. It is the purpose of this paper to indicate the frequency with which café-au-lait spots are to be found in normal unrelated persons, in persons with proved neurofibromatosis, and in the families of the latter. No attempt will be made in this paper to elaborate on the other clinical, genetic, or pathological manifestations of this protean disease.

DATA

The data on café-au-lait pigmentation reported here were derived from examination of (1) 6,853 inmates of four Michigan institutions (three homes for the mentally deficient and one hospital for epileptics), (2) 98 patients with proved neurofibromatosis and 10 of their young offspring or siblings suspected as having early forms of the disease, and (3) 137 normal relatives of persons in Group 2.

For the purposes of this study the only criterion added beyond those already mentioned to the definition of a café-au-lait spot was that of minimum size. Only those café-au-lait spots whose broadest diameter exceeded 1.5 cm. were recorded. It was realized that many true café-au-lait spots are smaller, but by imposing this limit accurate objective counts were possible and the risk of confusing the café-au-lait type of pigmentation with either the lentigo or the ephelis was materially reduced. Moreover, in order that the chance of error might be reduced to a minimum, all 7,098 persons were seen by one of us (F. W. C.).

Those persons having single or multiple lentigines or ephelides or a single area of pigmentation in which the possibility of either traumatic or actinic origin was suspected were not included.

COMMENT

The type and role of pigmentation in neurofibromatosis has occasioned considerable speculation. Siemens [6] maintained that a gross anatomical difference exists between the macular pigmentation to be found in neurofibromatosis and that found in the normal person. He contended that the café-au-lait spot found in neurofibromatosis is almost always smooth-bordered, whereas the macular pigmentation characteristic of the normal person is of irregular contour (the so-called nevus spilus). Fischer [7] and Saalfeld [8] have supported Siemens. Meirowsky,[9] on the other hand, has questioned the reality of this distinction. He holds that both types, as well as intermediate forms, are to be found not only in the normal person but also in the person with neurofibromatosis.

Among the 98 persons with neurofibromatosis reported in this study no characteristic type of delineation of the macular pigmentation was observed. A not uncommon finding was a considerable range of variation in the shape of the café-au-lait spots upon a single person with multiple areas of pigmentation. Furthermore, among the normal persons an equally large range of variation was found in the borders of the pigmented areas. These observations would support the view that there is no essential gross difference between the pigmentation found in the normal person and that found in persons with neurofibromatosis.

6. Siemens, H. W.: Zum Studium der Abortivformen der Recklinghausenschen Krankheit, Dermat. Ztschr. **46**:168, 1926; Über Pigmentflecke bei Recklinghausen-Kranken, Arch. Dermat. u. Syph. **151**:382, 1926.

7. Fischer, H.: Beitrag zur Recklinghausenschen Krankheit, Dermat. Ztschr. **42**:143, 1925.

8. Saalfeld, U.: Zur dermatologischen Statistik, Dermat. Ztschr. **52**:399, 1928.

9. Meirowsky, E.: Die Pigmentnaevi bei der Recklinghausenschen Erkrankung, in Handbuch der Haut-und Geschlechtskrankheiten, edited by J. Jadassohn, Berlin, Springer-Verlag, 1933, Vol. 4, Pt. 2, p. 671.

Stalmann [10] has observed the association of café-au-lait spots with (1) thickening of the nerves in the dermis, (2) an increase, in some instances, in the amount of connective tissue around these nerves, and (3) hypertrophy of hair follicles and of sebaceous and eccrine glands. These features led him to believe that the café-au-lait spot of neurofibromatosis could be differentiated on a histological basis from the macular pigmentation in normal persons. Lever,[11] Stout,[12] and McNairy and Montgomery,[13] on the other hand, have stated that the macular pigmented areas found in neurofibromatosis show only increased melanin formation. Histological material obtained in the present study was consistent with the findings of Lever, Stout, and McNairy and Montgomery. In the absence of positive evidence to support the belief that a histological difference does exist, it was concluded that there was no essential difference, either gross or histological, between the macular pigmentation found in normal persons and that found in those with neurofibromatosis.

TABLE 1.—*Distribution of the Number of Café-au-Lait Spots in Unrelated Persons Showing No Cutaneous Evidence of Neurofibromatosis*

Classification of Patients	Café-au-Lait Spots per Patient, No.						Patients Examined, No.
	0	1	2	3	4	5	
Institutionalized males	3,135	313	56	4	2	0	3,510
%	89.3	8.9	1.6	0.1	0.06	..	
Institutionalized females	3,028	268	36	7	2	2	3,343
%	90.6	8.0	1.1	0.2	0.06	0.06	
Total institutionalized males and females	6,163	581	92	11	4	2	6,853
%	89.9	8.5	1.3	0.16	0.06	0.03	
Male college students*	1,216	101	10	1	1	2	1,331
%	91.4	7.6	0.8	0.08	0.08	0.15	

* Unpublished data from Lerner and Fitzpatrick,[14] presented for comparison only.

FINDINGS

The Incidence of Café-au-Lait Spots Among Unrelated Persons with No Cutaneous Manifestations of Neurofibromatosis.—Among 6,853 institutionalized persons without cutaneous manifestations of neurofibromatosis 690, or 10.1±0.36%, were found to possess one or more café-au-lait spots on complete dermatological examination. The distribution of the number of café-au-lait spots among the latter persons is presented in Table 1. The difference, 1.3%, observed between the sexes in the frequency of café-au-lait pigmentation is not statistically significant.

To determine whether the frequency of café-au-lait spots differs between institutionalized and noninstitutionalized persons, these data were compared with those

10. Stalmann, A.: Nerven-, Haut-, und Knochenveränderungen bei der Neurofibromatosis Recklinghausen und ihre entstehungsgeschichtlichen Zusammenhänge, Arch. path. Anat. **289**:96, 1933.

11. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949, p. 365.

12. Stout, A. P.: Tumors of the Peripheral Nervous System, Sect. 2, Fascicle 6, in Atlas to Tumor Pathology, Armed Forces Institute of Pathology, 1949.

13. McNairy, D. J., and Montgomery, H.: Cutaneous Tumors of von Recklinghausen's Disease (Neurofibromatosis): Report of Histologic Study, Arch. Dermat. & Syph. **51**:384, 1945.

collected by Lerner and Fitzpatrick.[14] These workers observed café-au-lait spots in a frequency of 8.6±0.77% among 1,331 males examined at the time of admission to the University of Michigan. The difference, 2.1%, in the frequency of café-au-lait pigmentation between the institutionalized and the college males is on the borderline of statistical significance. Since most of this difference occurs in the frequency of persons with one café-au-lait spot, it is our opinion that this difference is probably spurious and attributable to minor variation in technique.

The Incidence of Café-au-Lait Spots Among Persons with Proved Neurofibromatosis.—Among 98 persons with neurofibromatosis 88, or 89.8±3.06%, were observed to have at least one café-au-lait spot. The finding that some 10.2% of persons with neurofibromatosis have no café-au-lait spots is contrary to the reports of some workers, who have stated that café-au-lait spots are a constant feature of this disease (Stalmann[10]).

To determine the diagnostic importance of the café-au-lait spot in neurofibromatosis, a distribution was made of the number of café-au-lait spots possessed by the 98 persons. These data are presented in Table 2. It will be noted that some 68.3% of the persons with neurofibromatosis had six or more café-au-lait spots.

TABLE 2.—*Distribution of the Number of Café-au-Lait Spots in Persons with Proved Neurofibromatosis*

	Café-au-Lait Spots per Patient, No.														Patients Examined, No.
	0-1	2-3	4-5	6-7	8-9	10-11	12-13	14-15	16-17	18-19	20-21	22-23	24-25	26+	
Males.....	8	2	4	2	5	8	7	4	2	2	4	0	0	2	50
Females....	7	6	4	1	4	4	5	4	2	5	3	1	0	2	48
Total.....	15	8	8	3	9	12	12	8	4	7	7	1	0	4	98
%.....	15.3	8.2	8.2	3.1	9.2	12.2	12.2	8.2	4.1	7.1	7.1	1.0	..	4.1	

As a consequence of this observation and the fact that not a single adult was found with six or more café-au-lait spots who did not also have neurofibromata, three young institutionalized persons (each of whom had a minimum of 10 café-au-lait spots) were suspected of having an early form of neurofibromatosis.

When the number of café-au-lait spots observed was compared with the distribution of neurofibromata, the impression was gained that the fewer the number of café-au-lait spots the more marked was the central involvement, as characterized by central nervous system, intrathoracic, or retroperitoneal tumors. Furthermore, it was observed that in the peripheral form of the disease, with late age of onset, and in the group of persons in whom the neurofibromata were localized in one segment of the body, café-au-lait spots were frequently lacking or present in small numbers. For example, among the 23 persons with three or fewer café-au-lait spots, no fewer than 17 (74%) had either the peripheral form of the disease, with late onset, marked central involvement, or a segmental distribution of the neurofibromata. This relationship between café-au-lait pigmentation and the distribution of the neurofibromata is indicated in Table 3. The largest group, of those with typical cutaneous tumors, showed no clinically obvious osseous changes and hence were not subjected to a roentgenologic bone survey. There remains a possibility

14. Lerner, A. B., and Fitzpatrick, T. B.: Unpublished data.

of minor osseous changes in these patients. For those persons with major, clinically recognizable, changes we have, in most instances, x-ray verification of this bony involvement.

A Comparison of the Number of Café-au-Lait Spots in Related Persons with Neurofibromatosis.—Among the 98 persons with neurofibromatosis it was possible to make 34 comparisons either of an affected parent with an affected offspring or of an affected sibling with an affected sibling. These 34 comparisons, which are presented in Figure 1, involved only 42 of the 98 persons with proved cases of the disease. Some features of these data are apparent on inspection. We note, for example, the infrequent association of an older sibling with few café-au-lait spots and a younger sibling with many areas of macular pigmentation. This observation would imply a positive association in the number of café-au-lait spots between sib and sib. To determine the significance of this apparent association, a correlation coefficient was calculated. This coefficient was found to be 0.584 between sib and sib and is statistically significant. A similar correlation coefficient obtained for the

TABLE 3.—*Relationship of Café-au-Lait Pigmentation to Distribution of Neurofibromata*

Distribution of Neurofibromata	Café-au-Lait Spots per Patient, No.					Total
	0-5	6-11	12-17	18-23	24+	
1. Cutaneous tumors with or without minor osseous changes	12	17	19	10	2	60
2. Cutaneous tumors with						
(a) Major osseous changes	7	5	4	2	2	20
(b) Central nervous system involvement	4	1	0	1	0	6
(c) Deep tumors	0	0	1	0	0	1
3. Central involvement without cutaneous tumors						
(a) Major osseous changes	0	1	1	1	0	3
(b) Central nervous system involvement	1	0	0	0	0	1
(c) Deep tumors	2	0	0	0	0	2
4. Segmental localization of cutaneous tumors	3	0	0	0	0	3
5. Cutaneous tumors with late age of onset	2	0	0	0	0	2
Total	31	24	25	14	4	98

parent-offspring relationship was not significant ($r = 0.117$), substantiating the impression gained from inspection of the data in Figure 1.

The existence of this correlation between affected siblings suggests the possibility of recognizing the "pretumorous" stage of neurofibromatosis. In the course of the family investigations associated with this survey, 10 persons were noted who were classified as having early forms of neurofibromatosis despite the absence of demonstrable tumors or other stigmata of the disease. The assumption that these persons have early forms of the disease was based on the similarity in degree of their macular pigmentation to that found in immediate relatives with proved neurofibromatosis (Fig. 2).

The Incidence of Café-au-Lait Spots Among Normal Relatives of Persons with Proved Neurofibromatosis.—The reliability of café-au-lait pigmentation as a diagnostic sign in recognizing neurofibromatosis is contingent upon the demonstration that the normal relatives of affected persons have an incidence and distribution in number of café-au-lait spots similar to that of unrelated normal persons. Examination of 137 immediate relatives (related as brothers and sisters or as parent and offspring) of the 98 affected persons revealed an incidence of

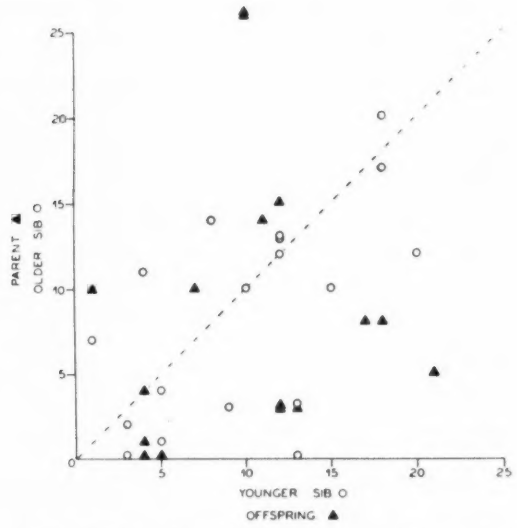

Fig. 1.—Relationship between numbers of café-au-lait spots in parent and offspring or in sib and sib in which both persons have proved neurofibromatosis.

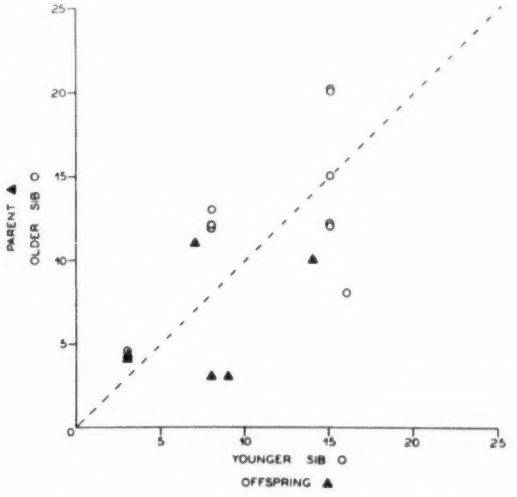

Fig. 2.—Relationship between number of café-au-lait spots in parent and offspring or in sib and sib in which one person has proved neurofibromatosis and the other is suspected to have an early form of the disease.

café-au-lait pigmentation of 13.1±2.89%. These data are presented in Figure 3 and Table 4. The marked discrepancy in numbers of males and females examined was due to the difficulties in examining the normal males, who were in many cases the wage earners for the family groups.

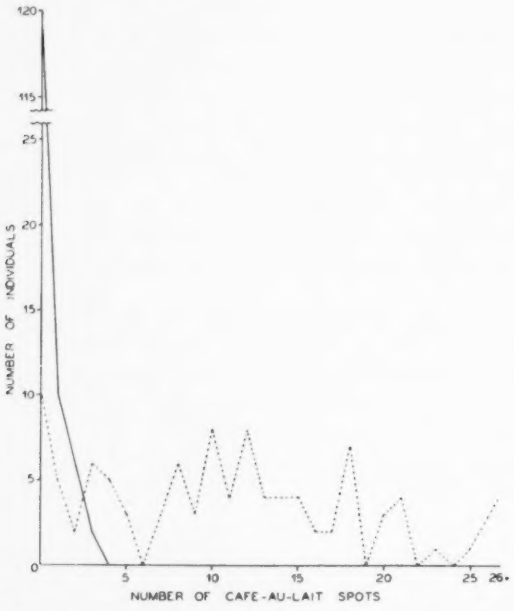

Fig. 3.—Distribution of café-au-lait spots among 98 persons with proved neurofibromatosis (broken line) and their 137 immediate relatives (solid line).

TABLE 4.—*Distribution of the Number of Café-au-Lait Spots Among Normal Relatives* of Persons with Classic Neurofibromatosis*

Classification of Patients	Café-au-Lait Spots per Patient, No.						Patients Examined, No.
	0	1	2	3	4	5	
Male relatives	47	5	3	1	0	0	56
%	83.9	8.9	5.4	1.8	..	..	
Female relatives	72	5	3	1	0	0	81
%	88.9	6.2	3.7	1.2	..	..	
Total male and female relatives	119	10	6	2	0	0	137
%	86.9	7.3	4.4	1.5	..	..	

* Related as brothers or sisters, parents or offspring, of persons with classic neurofibromatosis.

The difference observed in the incidence of café-au-lait spots in this group and in the institutionalized group is not statistically significant, nor does the incidence in this group differ significantly from that observed by Lerner and Fitzpatrick in college males. Thus, there is no evidence to indicate a greater incidence of macular pigmentation among the normal relatives of persons with neurofibromatosis than among normal unrelated persons.

The Frequency of Café-au-Lait Pigmentation in Tuberous Sclerosis and Encephalotrigeminal Angiomatosis.—Three of the congenital ectodermoses, von Recklinghausen's neurofibromatosis, Bourneville's tuberous sclerosis (epiloia), and encephalotrigeminal angiomatosis (Sturge-Weber syndrome) share similarities in their central nervous system manifestations, such as comparable roentgenologic changes,[15] epilepsy, and mental deficiency. It has also been suggested that these similarities may extend to include peripheral changes. Borberg,[16] for example, reports that café-au-lait pigmentation may be found in tuberous sclerosis, but our experience indicates that café-au-lait spots are no more frequent in patients with this disease or encephalotrigeminal angiomatosis than in the general population. In the examination of the institutionalized persons reported here, 53 persons with tuberous sclerosis and 12 with encephalotrigeminal angiomatosis were observed. Save for one person with tuberous sclerosis, these persons did not differ in the frequency of café-au-lait pigmentation from the others in the institutions. This single exception was a 13-year-old girl with 12 café-au-lait spots and multiple cutaneous tumors. Pathological examination of one of these tumors revealed a characteristic neurofibroma. A discussion of this girl will be reported elsewhere.[17]

The Clinical Significance of These Data.—These data permit the following generalizations of clinical import in cutaneous medicine:

1. Any person with more than six café-au-lait spots which exceed 1.5 cm. in broadest diameter must be presumed to have neurofibromatosis even in the absence of a positive family history. Proof of the exception rests upon the examining physician.

2. If a person has fewer than six café-au-lait spots and has no family history of the disease, the probability of involvement is related to the frequency of the particular number of café-au-lait spots in the general population. Thus, for example, since five café-au-lait spots are infrequent in normal persons, the probability that a person with five café-au-lait spots has neurofibromatosis is certainly higher than that of a person with one café-au-lait spot.

3. If a person has fewer than six café-au-lait spots but there exists a family history of neurofibromatosis, the probability of involvement is a function of the similarity in macular pigmentation between this person and the affected persons in the family. More reliance should be placed on comparison of sib to sib than on comparison of parent to offspring.

SUMMARY AND CONCLUSIONS

There is no gross or histologic feature which distinguishes the macular pigmentation, commonly known as café-au-lait spots, found in von Recklinghausen's neurofibromatosis from that found in normal persons.

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16. Borberg, A.: Clinical and Genetic Investigations into Tuberous Sclerosis and Recklinghausen's Neurofibromatosis: Contribution to Elucidation of Interrelationship and Eugenics of Syndromes, Acta psychiat. et neurol., Supp. 71, p. 3, 1951.

17. Schull, W. J., and Crowe, F. W.: The Neurocutaneous Syndromes in the M. Kindred, to be published.

Dermatological examination of 6,853 institutionalized patients without cutaneous manifestations of neurofibromatosis revealed 10.1% to have from one to five café-au-lait spots. This finding was comparable to that in a group of 1,331 college males.

Of 98 patients with proved neurofibromatosis, 89.8% were found to have one or more café-au-lait spots. Marked central involvement, segmental distribution of the neurofibromata, or late age of onset, in the case of peripheral forms of the disease, were more frequently observed among those persons having three or fewer café-au-lait spots than among the more pigmented persons.

A comparison of the number of café-au-lait spots in patients with neurofibromatosis revealed a statistically significant correlation between affected siblings. A comparable correlation was not obtained between parents and offspring.

Normal relatives of patients with proved neurofibromatosis demonstrated an incidence and distribution in the number of café-au-lait spots similar to that of unrelated normal persons.

A series of generalizations are proposed for applying these data to clinical cutaneous medicine.

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STUDIES ON THE AGING HEART

The "Normal" Heart in Old Age—Study Based on an Analysis of Eight Hundred Autopsies

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THE PHYSICIAN quite frequently has to decide whether certain changes the heart presents are within "normal" limits or beyond them. This is often a difficult decision to make in the younger person and it is more so in the old. And yet the decision has to be made, since the advice of the physician as to medication and as to ordering a different way of life and forecasting life expectancy will depend on it.

This report, the third in a series on the aging heart,[1] is concerned with the overall pathological and clinical findings in persons who have reached the age of 60 with no gross coronary artery disease or other heart ailment. Heart disease is not an inevitable accompaniment of old age. Newer research [2] has uncovered a few of the predisposing or etiological factors in arteriosclerotic heart disease or, specifically, coronary arteriosclerosis. The prospects for a better fundamental therapeutic and prophylactic approach are for the first time brighter. It was felt that detailed studies of those persons who have aged without acquiring heart disease might contribute further data toward solution of this problem.

In this study 800 consecutive autopsies of patients over 60 years of age were analyzed. Of the 800, 5%, or 40, showed no gross evidence of coronary arteriosclerosis, myocardial fibrosis, myocardial hypertrophy, or other heart disease. Table 1 shows the age and sex distribution of these 40 patients. Comparison with the figures of other workers is not productive, since practically all of them paid attention only to coronary arteriosclerotic disease and not to other cardiac ailments and also because pathological criteria and population samplings vary. Nevertheless we cite relevant data from the literature. Our series consists of patients who died in a public hospital for chronic diseases.

From the Second Medical Division of Goldwater Memorial Hospital, Service of Dr. Kaufman.

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With detailed microscopic study Willius and Smith [3] found only 0.3% of persons in the decade 60 to 69 years free of coronary arteriosclerosis. Levy and his associates [4] found sclerotic heart disease to be the cause of death in 25% of those over 65 years of age. Gordon, Bland, and White [5] found that 81.3% of those in the age group 61 to 80 years, and 95% in the age group 80 to 100 years, had coronary arteriosclerosis with a greater incidence found in higher economic groups. All these authors emphasize a greater incidence in men than in women. Ackerman, Dry, and Edwards [6] and White, Edwards, and Dry [7] have studied the degree of coronary sclerosis in men and women in different age groups. The degree of arteriosclerosis reaches a peak at the age decade of 50 to 59, with a rather constant level thereafter.

CLINICAL FINDINGS

Functional Capacity.—The functional capacity of the heart in all 40 patients was good. For none was there an antemortem diagnosis of congestive failure or a clinical note of diminished cardiac reserve. We have found that an anatomically normal heart performs its work in old persons just as efficiently as in the young.

TABLE 1.—*Age and Sex Distribution of Forty Patients over Sixty Years Old with No Cardiac or Coronary Artery Disease*

Age, Yr.	Men, No.	Women, No.
60-69	9	6
70-79	9	4
80-89	9	3

There are reports of chemical aging [8] and of heart failure due to nutritional deficiencies without anatomical deformity. These have not been encountered in our series.

Murmurs.—No diastolic murmurs were recorded in any of the 40 patients. In 10 patients systolic murmurs of moderate or loud intensity were heard. This conforms with the accepted criterion that systolic murmurs in themselves are not indicative of heart disease.[9] An associated factor which might account for the murmurs heard in one patient was heart block.

3. Willius, F. A., and Smith, H. L.: A Study of Coronary and Aortic Sclerosis Incidence and Degree in 5060 Consecutive Post-Mortem Examinations, Proc. Staff Meet., Mayo Clin. **8**:140, 1933.

4. Levy, R. L.; Bruenn, H. G., and Kurtz, D.: Facts on Disease of the Coronary Arteries, Based on a Survey of the Clinical and Pathologic Records of 762 Cases, Am. J. M. Sc. **187**:376, 1934.

5. Gordon, W. H.; Bland, E. F., and White, P. D.: Coronary Artery Disease Analyzed Post-Mortem with Special Reference to the Influence of Economic Status and Sex, Am. Heart J. **17**:10, 1939.

6. Ackerman, R. F.; Dry, T. J., and Edwards, J. E.: Relationship of Various Factors to the Degree of Coronary Atherosclerosis in Women, Circulation **1**:1345, 1950.

7. White, N. K.; Edwards, J. E., and Dry, T. J.: The Relationship of the Degree of Coronary Atherosclerosis with Age, in Men, Circulation **1**:645, 1950.

8. Nechren, T. H., and McKee, F.: Cardiac Failure in a "Normal Heart." Ann. Int. Med. **33**:1485, 1950.

9. Levine, S. A., and Harvey, W. P.: Clinical Auscultation of the Heart, Philadelphia, W. B. Saunders Company, 1950.

Electrocardiographic Findings.—Electrocardiographic tracings were made in 35 of the 40 patients. These were made mainly with Leads I, II, III, and cF_4 and were interpreted according to criteria of the New York Heart Association.[10] Several recent studies[11] have been published of more detailed analyses with unipolar or esophageal leads on large numbers of aged patients. The authors of these emphasize that studies not correlated with postmortem findings are subject to error. Many clinically "normal" hearts will show coronary arteriosclerosis and/or myocardial fibrosis at necropsy. We did find three cases with inversion of T waves in Leads I and cF_4. In two of these three, however, there was associated anoxemia and cerebral accident, and in one severe pneumonia. There were five with auricular fibrillation and one with Grade 1 heart block. These were chemical and physical variations not attended by anatomical changes.

X-Ray Findings.—Teleroentgenograms of 36 of the 40 patients were available for study. Cardiac contours were reported as normal in 34. In two the roentgenologist reported slight accentuation of the left ventricle. This study, as have past studies, emphasizes the general clinical accuracy of x-ray and fluoroscopic investigation of cardiac size and shape.

Blood Pressure.—Blood pressures were under 150/100 in 35 of the 40 patients. Readings of 180 to 150/80 to 70 and 180 to 170/70 to 60, in two patients, may be considered of little significance. There were two patients with mild essential hypertension, 180/110 and 160-146/105-90. Both showed nephrosclerosis and cerebral arteriosclerosis but not coronary arteriosclerosis. One additional hypertensive patient, with blood pressure of 170/110, showed chronic pyelonephritis and cerebral arteriosclerosis. Hypertension of any degree was almost always accompanied by coronary sclerosis.

Racial and Nutritional Factors.—Much of the newer knowledge of arteriosclerosis concerns racial and nutritional factors.[12] As was said before, we do not have statistically significant data on these factors in this series. It is interesting that, even at death, two of the women and three of the men were described as obese. This dovetails with the generally held view that hypertension is more frequent in those who are overweight and, specifically, with the finding of Wilens[13] that advanced arteriosclerosis is about twice as common in the obese.

Cause of Death.—The causes of death in the 40 patients are given in Table 2. Associated illnesses not causing death are given in Table 3. We wish to note that there was no case of diabetes. Another finding in this group was that those patients who do not suffer from or do not die of heart disease die mostly of malignant neoplasms, cerebral accidents, or ailments of the kidney.

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10. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York, New York Heart Association, 1945.

11. Harkin, J. C., and Beber, M.: The Electrocardiogram in Aged Individuals, J. Gerontol. (Supp. to No. 3) **6**:98, 1951. McNamara, R. J.: Study of Electrocardiogram in Persons over 70, Geriatrics **4**:150, 1949. Hagen, P., and Freeman, Z.: The Electrocardiogram in Old Age, M. J. Australia **1**:499, 1950.

12. Snapper, I.: Chinese Lessons to Western Medicine, New York, Interscience Publishers, Inc., 1941. Also footnotes 2, 6, 7, 13.

13. Wilens, S. L.: Bearing of the General Nutritional State on Atherosclerosis, Arch. Int. Med. **79**:129, 1947.

Arteriosclerosis of Other Organs.—Our findings in this report have been stated before, but their significance cannot be overemphasized. In 6 of the 40 patients death was directly related to arteriosclerosis of other organs.[14] Of these six there were two with cerebral hemorrhage and four with cerebral arteriosclerosis and multiple brain softenings. In addition, cerebral arteriosclerosis was found in 6 other patients (of the 30 in which brain necropsy was permitted); 27 of the 40 showed renal arteriosclerosis or renal arteriolonephrosclerosis of slight or moderate degree.

TABLE 2.—*Causes of Death in Forty Patients over Sixty Years Old*

Causes of Death	Patients, No.
Carcinoma and leukemia	15
Cerebral accident	6
Chronic neurological disease	4
Postoperative acute abdominal condition	4
Pyelonephritis	4
Pneumonia	2
Pulmonary emboli	1
Meningitis	1
Tuberculosis	1
Cirrhosis of liver	1
Rheumatoid arthritis with cachexia	1

TABLE 3.—*Diseases in Forty Patients over Sixty Years Old Which Were Not the Cause of Death*

Associated Diseases	Patients, No.
Nephrosclerosis	15
Urinary infection	10
Cholelithiasis	10
Pneumonia	7
Tuberculosis	6
Cerebral sclerosis	6
Hypertrophy of prostate	4
Fatty liver	4
Emphysema	3
Hepatitis	3
Pleuritis	3

COMMENT

Usually two approaches are used to determine the range of changes found in physiological aging of the heart as distinguished from the changes which should be designated as pathological.

The first approach is the clinical; its aim is to gather data on a certain number of persons who on examination can be considered "normal" and to determine what are the measurable findings on inspection, auscultation, x-ray, and electrocardiogram, and investigation of blood pressure, pulse, venous pressure, circulation time, heart sounds, functional capacity, and other factors. This is a statistical approach at its best, and its purpose is to get the imaginary picture of the average "normal" person. Every statistical approach, especially if based on small number of cases, as it usually is, might be misleading just for that reason. Another source of error is that any

14. Gavey, C. J.: Cardiology of Old Age (Goulstonian Lecture), Lancet **2**:725, 1949.

person might be "normal" by the accepted clinical criteria and still have coronary or other cardiac diseases found only at autopsy. The second approach is through postmortem data. The question here is what are the measurements of the weight and size of the heart, what are the measurements of the valve orifices, walls of chambers, and diameters of coronary arteries in those hearts which do not show macroscopic and microscopic pathological changes. This method is inadequate unless it brings the pathological data into relationship with the clinical examination, history, laboratory data, and, last but not least, the functional capacity of the heart. This has been done in only a few publications.

We have chosen to find the cause of death and to study the noncardiac and cardiac pathological and premortem clinical findings in a series of patients who neither clinically nor anatomically presented any evidence of cardiac disease. The analysis of the data showed that the cause of death was carcinoma or leukemia in 15 patients, cerebral accident in 6, chronic neurological disease in 4, postoperative acute abdominal condition in 4, pyleonephritis in 4, pneumonia in 2, pulmonary emboli in 1, meningitis in 1, tuberculosis (in lungs) in 1, cirrhosis in 1, and rheumatoid arthritis with cachexia in 1. Associated diseases were, in order of their frequency, nephrosclerosis, urinary infection, cholelithiasis, pneumonia, tuberculosis, cerebral sclerosis, hypertrophy of the prostate, fatty liver, emphysema, hepatitis, and pleuritis.

The most important premortem clinical changes found on physical examination and from x-ray studies, such as those of functional capacity, murmurs, blood pressure, and arteriosclerosis of organs other than the heart, were summarized above under the heading "Clinical Findings." Other clinical observations in this group of persons with normally aging hearts can be added. The veins were often dilated; venous pressure increased in the absence of heart failure. The heart sounds were frequently faint, because of the senile changes in heart muscle, especially in persons above the age of 60. The second sound of the aorta, however, was often accentuated in those with pronounced hypertension in the systemic circuit, and the pulmonic second sound was greater than the aortic second sound in cases of hypertension in the pulmonary circuit. Also the first heart sound may have been loud (in the absence of mitral stenosis) in fever or after emotional stress. The systolic murmurs which are so often present in the aged without heart disease are generally attributed to the less accurate closing of the valves or to tortuousness and dilatation of the aorta. Sprague pointed out that if calcified plaques are found by x-ray examination or at autopsy to protrude into the lumen of the aorta, rough loud systolic murmurs can often be heard clinically.

In this study electrocardiograms were made in 35 of the 40 patients. We used mainly Leads I, II, III, and cF_4. Our later unipolar lead electrocardiograms, taken on elderly patients without heart disease, show premature contractions, decreased voltage of P, QRS, and T waves, left axis shift, and prolonged QRS, P-R, and ST components.

Teleroentgenograms were taken in 36 of the 40 cases. Thirty-four of these were normal; 2 were interpreted as showing minor accentuation of the left ventricle. This agreement between the negative pathological, functional, and roentgenological findings indicates another valuable method for making a differential diagnosis between the normal and the abnormal heart in the aging person.

SUMMARY AND CONCLUSIONS

In a study of 800 consecutive autopsies of patients over the age of 60 years, 5%, or 40, were found who did not show any gross evidence of coronary arteriosclerosis, myocardial fibrosis, hypertrophy, or other heart disease. Neither did any of these patients present significant premortem clinical, anatomical, or functional defects on physical, roentgenological, or electrocardiographic examination. The congruity of the data obtained by the different methods of examination is considered significant. Two conclusions can be drawn: 1. Even after the age of 60 most anatomically normal hearts are usually normal functionally too. 2. Clinical, roentgenological, and electrocardiographic methods of study, if critically appraised, usually give a fairly accurate differentiation between the "normal" and the "abnormal" heart in the aging person.

TREATMENT OF CENTRAL NERVOUS SYSTEM CRYPTOCOCCOSIS

Laboratory Studies

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THE PROBLEM of therapy in infections with Cryptococcus neoformans remains unsolved. In a previous publication [1] the use of a wide variety of drugs in the treatment of central nervous system cryptococcosis was reviewed, with particular emphasis on the results obtained with fever therapy, protoanemonin, Bacillus subtilis derivatives and cycloheximide (Acti-Dione). Experience with the latter drug was summarized and its use in four cases of central nervous system cryptococcosis reported with improvement in one case (the patient subsequently dying) and perhaps a cure in another; the latter patient has been followed for one and one-half years without relapse of the disease. Wilson and Duryea [2] have likewise reported a "cure" with cycloheximide. However, in other cases of cryptococcic meningitis cycloheximide appeared to have had no effect upon the course of the infection. Other agents have since been reported as having an inhibitory or fungicidal effect against C. neoformans; namely, prodigiosin,[3] fungicidin,[4] ethyl vanillate,[5] polymyxin B,[6] and 3569,[7] an antifungal antibiotic isolated from a culture of Streptomyces aureus.

C. neoformans, although a fungus, lends itself admirably to bacteriological techniques. Reproducible sensitivity tests can be performed in vitro, using the tube dilution method. As in the case of bacteria, however, there are definite limitations in the application of in vitro sensitivity data to human infection, in that clinical

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1. Carton, C. A.: Treatment of Central Nervous System Cryptococcosis: A Review and Report of 4 Cases Treated with Actidione, Ann. Int. Med. **37**:123-154, 1952.

2. Wilson, H. M., and Duryea, A. W.: Cryptococcus Meningitis (Torulosis) Treated with a New Antibiotic, Actidione, A. M. A. Arch. Neurol. & Psychiat. **66**:470-480, 1951.

3. Lack, A. R.: Personal communication to the author.

4. Hazen, E. L., and Brown, R.: Fungicidin, an Antibiotic Produced by a Soil Actinomycete, Proc. Soc. Exper. Biol. & Med. **76**:93-97, 1951.

5. Blank, H.: Personal communication to the author.

6. (*a*) Searle, D. S.: Personal communication to the author. (*b*) Quan, S.: Personal communication to the author. (*c*) Sweigert, C. F.: Personal communication to the author. (*d*) Eiben, R. M.: Personal communication to the author.

7. Raubitscheck, F.; Acker, R. F., and Waksman, S. A.: Production of an Antifungal Agent of the Fungicidin Type by Streptomyces Aureus, Antibiotics & Chemother. **2**:179-183, 1952.

therapeutic results do not always parallel laboratory antibiotic sensitivity tests.[8] This discrepancy has been particularly apparent in the studies with cycloheximide. In vitro this drug will inhibit C. neoformans in concentrations of 0.2 to 5.0 γ per cubic centimeter, yet in vivo, with apparently adequate dosage, the drug will in many cases have no effect on the clinical infection caused by a proved sensitive strain. In addition, in the presence of other drugs C. neoformans may be insensitive in the "accepted" sensitivity range for bacteria but will be inhibited by concentrations of 200 γ per cubic centimeter or more. The latter concentration is usually indicative of an "insensitive" micro-organism, but in animal experiments such a drug may prove to be of therapeutic value. It would seem that new drugs should be tried in animals, and, conversely, a negative result in animals (such as with cycloheximide[9]) should not deter one from making a clinical trial if adequate toxicity studies are available. These points are stressed so that the sensitivity data described below may be viewed in their proper perspective.

In view of the high mortality of central nervous system cryptococcosis, as previously noted,[1] it was thought profitable to study various agents for possible action against C. neoformans.[10] In vitro tests were performed comparing the effects of these single agents (as well as combinations of drugs) on a standard human pathogenic strain of C. neoformans; preliminary animal studies were also undertaken.

MATERIALS AND METHODS

Source of Agents.—Twenty-nine agents have been tested for activity against C. neoformans, the source of supply being indicated in Table 1. Water-soluble drugs were dissolved in agents recommended or were ground up and suspended in water or in aqueous Vehicle No. 1 (Merck). Dilutions of all drugs were made in the broth to be inoculated, fresh pipettes being used for each transfer of drugs in suspension.

C. Neoformans Strain.—One strain, Rh-1474, was used throughout this work. It was isolated, in February, 1947, from a patient reported elsewhere[1] and was supplied through the courtesy of Dr. Rhoda Benham. As noted previously,[1] this strain was intermediate in its range of sensitivity to cycloheximide when compared with numerous other strains. The patient died in May, 1952, five years after the central nervous system infection was recognized.

Media.—1. Broth: Two types of broth were used, (*a*) fresh beef heart infusion broth containing 2% honey, with an unadjusted pH averaging 5.6 to 5.7 and (*b*) a yeast extract medium described by Whiffen[11] containing yeast extract (Difco) 0.25%, glucose 1%, and $KHPO_4$ 0.1%, adjusted to pH 6.0. The latter was used for most assays because the organism grew rapidly in it and the medium was clear, making possible more accurate end-point determinations.

2. Agar: The Difco yeast medium with 2% agar was used for all plating tests. For monthly transfers of stock cultures Sabouraud's dextrose agar slants were used.

8. Laboratory Control of Antibiotic Therapy, Editorial, J. A. M. A. **147**:1360-1361, 1951. Sensitivity of Bacteria to Antibiotics, Editorial, New England J. Med. **245**:868-870, 1951. An Interim Statement of Laboratory Determination of Bacterial Sensitivity to Antibiotics, Lederle Laboratories Division, American Cyanamid Company, 1952.

9. Fisher, A. M.: The Clinical Picture Associated with Infections Due to Cryptococcus Neoformans (Torula Histolytica): Report of 3 Cases with Some Experimental Studies, Bull. Johns Hopkins Hosp. **86**:383-414, 1950.

10. Most of these compounds had been preliminarily screened by the various drug companies, through whose courtesy the drugs were supplied (Table 1).

11. Whiffen, A. J.: Production, Assay and Antibiotic Activity of Actidione, Antibiotic from Streptomyces Griseus, J. Bact. **56**:283-291, 1948.

Culture Standardization.—The following technique of standardizing the number of organisms [12] was applied to both in vitro and in vivo tests. The growth of the fungus incubated for 48 hours at 37.5 C. on Sabouraud's agar slants was washed off with sterile distilled water and centrifuged for 25 minutes at 1700 rpm. The volume of packed cells was then measured and diluted in 250 parts of distilled water. This suspension was further diluted to concentrations of 10^{-4}, 10^{-5}, and 10^{-6}, plates were poured, and counts of the viable organisms were made. The stock 1:250 dilution contained from 9×10^6 to 14×10^6 organisms per cubic centimeter. This variation in numbers produced no significant difference in assay end points. For tube assays the stock suspension was used in a dilution of 2.5×10^{-5} in broth; for in vivo testing 0.2 cc. of a 10^{-3} dilution was inoculated in mice.

Tube Dilution Technique.—The tube dilution method was used (1) to test in vitro sensitivity to single drugs, (2) to test the mode of action of some of these drugs, (3) to check the possible development of resistance of the strain to cycloheximide and polymyxin B in vivo, and (4) to test the effect of certain combinations of drugs.

For in vitro sensitivity work, 10-fold dilutions of the drugs were first tested, the range being subsequently narrowed according to preliminary results. Subsequent test solutions within the desired range were prepared as follows: An initial dilution of the drug was prepared with a concentration tenfold greater than desired final concentration. Then 0.5 cc. of this initial drug dilution was added to 4.0 cc. of broth to which was also added 0.5 cc. of a 2.5×10^{-4} dilution of the standardized C. neoformans, so that the final volume was 5.0 cc., or a 1:10 dilution. Tubes run in duplicate were incubated at 37.5 C. and read at 72 hours. All preliminary assays of new drugs were controlled by a cycloheximide assay. The end-point was taken to be the tube without any visible growth, and the drug concentration in that tube was considered to be the minimal inhibitory concentration measured in micrograms per cubic centimeter.

To check the mode of action of drugs having minimal inhibitory concentration below 10 γ per cubic centimeter, a modification of the method described by Emmons [13] was used, in which subcultures were made in agar from the end-point tubes, the samples being diluted 30 times in the plates (e. g., 0.5 cc. sample plus 14.5 cc. agar). If the drug in the dilution tested sterilized the culture, the effect was considered fungicidal; if colonies grew out, the effect was considered fungistatic. Negative plates were kept for one week before being discarded.

Resistance studies of strains of C. neoformans recovered from mice which had been treated with both cycloheximide and polymyxin B were performed according to the end-point method described above after the strains had been subcultured on Sabouraud's agar slants.

To determine the type of effect which certain drugs in combination have on each other, the end-points of tube assays were interpreted according to definitions and general methods described by Bliss, Warth, and Long.[14] If the end-point tube contained a combined minimal inhibitory concentration of the drugs that was between 0.9 and 1.2, the effect of one drug upon another was considered to be an additive one; if below 0.9, synergistic; if above 1.2, either antagonistic or ineffective.

The results obtained by this method for polymyxin B and cycloheximide were further checked by a growth study (patterned after those of Bliss and his associates [14]) in which the multiplication rate of the organism in the presence of one or both of these drugs was tested by comparing original inocula counts to colony counts from drug dilution tubes incubated for 1, 4, 24, 48, 72, and 192 hours after inoculation. The tubes from which the plating samples were taken contained the same final concentration as those used in other assays but in a 2.0 cc. final volume. Samples were diluted 30 times in agar, and negative plates were kept for one week before being discarded. Results were interpreted by comparing the growth curves obtained by plotting the number of colonies logarithmically against the time of plating for incubation. Curves

12. Hazen, E. L.: Personal communication to the author.

13. Emmons, C.: Fungicidal and Fungistatic Agents: Proposed Method for Testing Fungicides Against Trichophyton, Am. J. Pub. Health **35**:844-846, 1945.

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TABLE 1.—*Agents Tested Against Cryptococcus Neoformans*

Grouping			Toxicity †		
Agent	M. I. C.*	Characteristics	Acute, LD_{50}	Chronic-Subacute	Source of Agent
Low m. i. c. water-soluble agents					
Cycloheximide (Acti-Dione)	0.35 γ/cc. fungistatic	Antibiotic from Streptomyces griseus, diketone, water soluble	150 mg./kg. s. c.	Weight loss with 5 mg./kg./day s. c.	Upjohn No. 8613-S
Polymyxin B (Acrosporin)	3.0 γ/cc. fungicidal	Antibiotic from Bacillus polymyxa, basic polypeptide, water soluble	82.5 mg./kg. s. c.	Permanent nephrotoxic effects with 5.0 mg./kg./day s. c.	Burroughs-Wellcome
Low m. i. c. water-insoluble agents					
U-0579	3.0 γ/cc. fungicidal	Nitrosulfone, non-water-soluble, suspended in Aqueous Vehicle 1 (Merck), then diluted suspension	386 mg./kg. s. c.	.....	Upjohn 400-EHL-92
Compound 77	5.0 γ/cc. fungicidal	Tetrahydrofluorononone, non-water-soluble, diluted water suspension	3/10 die with 100 mg./kg. p. o.‡ every day for 10 days	.....	Organon Lot No. 152
Rimocidin	5.0 γ/cc. fungicidal	Non-water-soluble, suspended in Aqueous Vehicle 1 (Merck), then diluted suspension	.....	.....	Pfizer Lot No. 519233
Thiolutin	5.0 γ/cc. fungicidal	Non-water-soluble, suspended in Aqueous Vehicle 1 (Merck), then diluted suspension	.....	.....	Pfizer Lot No. 249-268
P-968	5.0 γ/cc.	Non-water-soluble, dissolved in acetone then diluted	210 ± 16 mg./kg. i. p.‡	.....	Commercial Solvents Corp.
Enzymes					
Streptokinase-Streptodornase (Varidase)	150 units/cc. streptokinase, honey broth only	Fibrinolytic enzyme from Group C streptococci	.....	Questionable pyrogenic or allergic reaction in human	Lederle
Desoxyribonuclease (crystallized)	> 100 γ/cc.	Enzyme which acts on desoxyribonucleoprotein	.....	.....	Worthington Biochemical Lab. No. D-277
Hyaluronidase (Wydase)	10 T. R.U./cc.	Enzyme hydrolysing polysaccharide hyaluronic acid	.....	No toxic or allergic reactions with maximum human dose of 150 T. R. U.‡	Wyeth

Compounds possibly similar to cycloheximide					
Mysoline	>100 γ/cc.	Phenylethylhexohydropyrimidinedione, non-water-soluble, diluted aqueous suspension	.....	.....	Ayerst, McKenna & Harrison
Paramethadione (Paradione)	>1 mg./cc.	Water-insoluble, aqueous dilution of supernatant of alcohol solution	.....	.....	Abbott
Trimethadione (Tridione)	>1 mg./cc.	Water-soluble, 3, 5.5 trimethyloxazolidine-2,4-dione	.....	.....	Abbott
Dimedione	>1 mg./cc.	3 ethyl-5,5 dimethyloxozolidine-2,4 dione, non-water-soluble, diluted aqueous suspension	.....	.....	Merck
High m. i. c. agents with known in vitro activity					
Ethyl vanillate	400 γ/cc.	Non-water-soluble, aqueous dilution of supernatant of acetone solution	.....	.....	Squibb
Antimonial Ro-2-3094	1.5 mg./cc.	Dietranolamine salt of a stibonic acid, water-soluble	590 mg./kg.	50 mg./day × 21 well tolerated	Hoffman LaRoche Control No. N-99V-1-1090
Other high m. i. c. agents					
A-4171	25 γ/cc.	Chlorinated aryl alkamine ether hydrochloride, water-soluble	200-300 mg./kg. i. p.	Some irritation due to anesthetic properties	Abbott
A-6652	>500 γ/cc.	Aryl alkamine, ether quaternary ammonium salt, water-soluble	75 mg./kg. i. p.	.....	Abbott
Marsalid	>1 mg./cc.	Isopropyl derivative of isonicotinic acid hydrazide, water-soluble	732 mg./kg. s. c.	Growth retarded, white and red blood cell changes; slight liver, kidney, and spleen changes	Hoffman-LaRoche
Darvisul	2.5 mg./kg.	Brand of phenosulfazole solution, 25% soluble in water (w/v)	.....	.....	Lederle No. 7-8322
P-1097	8 γ/cc.	.....	.....	.....	.....
P-649	10 γ/cc.	.....	72 mg./kg. i. p.	.....	.....
P-957	10 γ/cc.	.....	104 mg./kg. i. p.	.....	.....
P-597	20-30 γ/cc.	None water-soluble, aqueous dilutions made of supernatants of acetone solutions	347 ± 45 mg./kg. i. p.	.....	Commercial Solvents Corp.
P-1076	20-40 γ/cc.		96 mg./kg. i. p.		
P-750	20-40 γ/cc.		110 mg./kg. i. p.		
P-960	50-100 γ/cc.	.....	32 mg./kg. i. p.	.....	.....
P-594	100 γ/cc.	.....	195 ± 38 mg./kg. i. p.	.....	.....
P-621	100 γ/cc.	.....	2150 ± 11 mg./kg. i. p.	.....	.....

* Minimal inhibitory concentration; Cryptococcus neoformans strain Rh 1474 was used.
† Mouse data, unless otherwise noted. Data obtained from drug companies.
‡ Abbreviations are as follows: s. c., subcutaneously; p. o., by mouth; i. p., intraperitoneally; T. R. U., turbidity-reducing unit.

of combinations (totaling 1 minimal inhibitory concentration or less) falling below those of double amounts of each drug alone (1 minimal inhibitory concentration) denoted synergism; curves coinciding with single drug curves denoted no effect.

In Vivo Tests.—Infected Rockland-Swiss mice weighing 18 to 22 gm. were used for protective and therapeutic tests with cycloheximide and polymyxin B, alone and in combination. The mice were infected by intravenous inoculation via the tail vein with a distilled water suspension containing 5 to 8 $\times$ 10^6 organisms. The drugs, diluted in isotonic sodium chloride solution, were injected subcutaneously, the dosage being determined by the acute and chronic toxicity data presented in Table 1. Death caused by cryptococci was established by India-ink smears of brain tissue and by brain cultures on Sabouraud's agar.

RESULTS

In Vitro Sensitivities Measured as Minimal Inhibitory Concentration.—Table 1 lists the results of the tube assays for minimal inhibitory concentration of individual drugs. On the basis of growth observations made after 72 hours' incubation, the antibiotics cycloheximide and polymyxin B are the most active of the water-soluble agents tested. Of the water-insoluble agents, U-0579 (Upjohn), Compound 77 (Organon), thiolutin and rimocidin (Pfizer), and P-968 and P-1097 (Commercial Solvents) have the most pronounced activity, approaching or equaling that of polymyxin B. The assays with enzymes proved difficult to interpret, since the streptokinase and streptodornase mixture (Varidase, Lederle) caused inhibition in honey broth but not in yeast-extract broth. Therefore, assays were carried out with hyaluronidase (Wydase) and desoxyribonuclease alone. Since hyaluronidase caused inhibition to an equal extent in both broths and desoxyribonuclease caused none in either of the dilutions tested, the discrepancy was assumed to be due to the kinase or to some impurity in the mixture.

Mode of Action.—Subcultures to agar pour plates from end-point tubes of assays of several drugs indicated that rimocidin, thiolutin, U-0579, Compound 77, and polymyxin B are fungicidal in their action, whereas cycloheximide is fungistatic. The former drugs in minimal inhibitory concentration amounts sterilized the cultures in 72 hours, but the cultures in tubes with cycloheximide grew out readily after prolonged incubation as well as in pour plate subcultures.

Resistance Studies.—Data concerning resistance is sparse, but two observations deserve mention. 1. Two different isolates from the same patient, R. H. 1474 and 1499-43, taken five years apart, showed identical sensitivity to cycloheximide, despite the use of large therapeutic doses of cycloheximide in the interim period. The only noticeable difference between these two strains was that the 1499-43 strain grew out more slowly than the original culture. 2. Strains isolated at death from mice infected with the 1474 strain and treated with large doses of polymyxin B and cycloheximide showed no change in response to the minimal inhibitory concentration testing of either drug.

Effect of Drug Combinations.—The problem of the synergistic action of antibiotics against bacteria has been ably discussed by Jawetz and his co-workers [15] and

15. (*a*) Jawetz, E.: Antibiotic Synergism and Antagonism: Review of Experimental Evidence, A. M. A. Arch. Int. Med. **90**:301-309, 1952. (*b*) Jawetz, E., and Gunnison, J. B.: Studies on Antibiotic Synergism and Antagonism: A Scheme of Combined Antibiotic Action, Antibiotics & Chemother. **2**:243-248, 1952. (*c*) Jawetz, E.; Gunnison, J. B.; Bruff, J. B., and Coleman, V. R.: Studies on Antibiotic Synergism and Antagonism: Synergism Among 7 Antibiotics Against Various Bacteria in Vitro, J. Bact. **64**:29-39, 1952.

others.[14] Table 2 summarizes the effects achieved against Cryptococcus neoformans when drugs were combined in tube dilution assays. Polymyxin B and cycloheximide, each with a low minimal inhibitory concentration in its own right, each appeared to potentiate the action of the other drug, the combination being synergistic.[14] Table 3 shows that the increase in activity was twofold for polymyxin B and eightfold for cycloheximide. The Compound 77-cycloheximide mixture was also synergistic. Other mixtures tested had an additive effect on each other, e. g., actidione with

TABLE 2.—*Effect of Combinations of Antifungal Agents, As Determined by 72-Hour Tube Dilution End-Point Method (After Bliss, Warth, and Long [14])*

Combination		Growth				Growth		Interpretation (Effect on First Agent)
		+		−		+	−	
		M.I.C. of Each Agent, % *				Total M.I.C. in Combination, % †	‡	
Poly §	Acti	0.03	0.57	0.03	0.86	0.60	0.89	Synergistic
Acti	Poly	0.07	0.33	0.07	0.67	0.40	0.74	Synergistic
Acti	Cpd 77	0.23	0.20	0.23	0.40	0.43	0.63	Synergistic
Cpd 77	Acti	0.40	0.12	0.40	0.23	0.52	0.63	Synergistic
Acti	Vari	0.06	0.67	0.06	0.80	0.73	0.86	Synergistic
Vari	Acti	0.67	0.23	0.67	0.43	0.90	1.07	Additive
Poly	Vari	0.17	0.67	0.17	0.80	0.84	0.97	Additive
Vari	Acti	0.67	0.17	0.67	0.33	0.84	1.00	Additive

* 1 m.i.c. (minimal inhibitory concentration) = 100% = 0.35 γ per cubic centimeter for cycloheximide; therefore, 0.57 m.i.c. = 57% = 0.2 γ per cubic centimeter for cycloheximide.
† Largest amount of drug which can be used without causing inhibition.
‡ Least amount necessary to inhibit.
§ The meanings of the abbreviations are as follows: Poly, Polymyxin B (m.i.c. 3.0 γ per cubic centimeter); Acti, cycloheximide (Acti-dione) (m.i.c. 0.35 γ per cubic centimeter); Cpd 77, Compound 77 (m.i.c. 5.0 γ per cubic centimeter); Vari, streptokinase-streptodornase (Varidase) (m.i.c. 150 units per cubic centimeter in terms of streptokinase).

TABLE 3.—*Effect of Combinations of Cycloheximide (Acti-Dione) and Polymyxin B in Vitro*

Poly B,* γ/Cc.	Cycloheximide,† γ/Cc.								
	0.35	0.3	0.2	0.15	0.1	0.08	0.04	0.025	Control
3.0	C‡	C	C	C	C	C	C	C	CS
2.0	C	C	C	C	C	C	C	C	+
1.0	C	C	C	C	CS	CS	S	+	+
0.5	S	S	+	+	+	+	+	+	+
0.1	S	S	+	+	+	+	+	+	+
Control	S	+	+	+	+	+	+	+	+

* Polymyxin B, minimal inhibitory concentration 3.0 γ per cubic centimeter.
† Minimal inhibitory concentration 0.35 γ per cubic centimeter.
‡ The meanings of the abbreviations are as follows: C, cidal effect when negative cultures were plated after eight days' incubation; S, static effect when negative cultures were plated after eight days' incubation; CS, primarily cidal, as very few organisms grew out; +, 72 hour results on basis of visual growth.

streptokinase and streptodornase, and polymyxin B with streptokinase and streptodornase, except that the effect of streptokinase and streptodornase on cycloheximide was synergistic. Since the enzymes are not drugs per se, this interpretation may not be valid, but they do not inhibit the activity of either cycloheximide or polymyxin B in vitro.

The multiplication-time curves derived from a growth study of the 1474 strain in the presence of polymyxin B and cycloheximide alone and in combination substantiate the synergism interpretation of the 72-hour tube assay and end-point

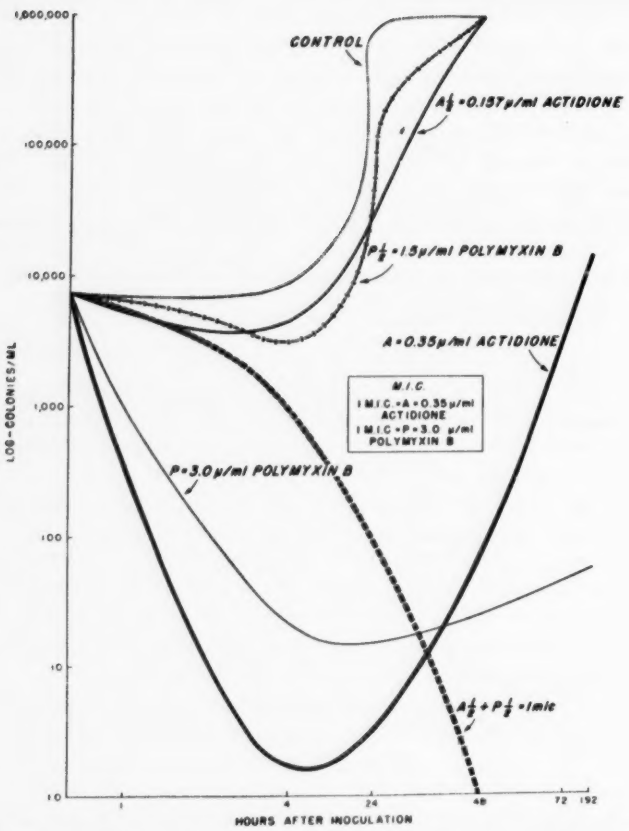

Chart 1.—Multiplication-time curve for Cryptococcus neoformans (Strain RH 1474) in presence of varied combinations of cycloheximide (Acti-Dione) and polymyxin B to show synergistic action of these drugs.

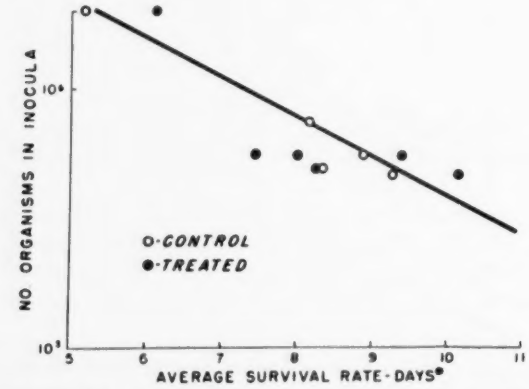

Chart 2.—Relationship between average survival rate-days of control mice and size of inocula. (Survival rate-days are determined by adding total number of days survived by all mice and dividing by number of mice.)

readings (Chart 1). Table 3 shows which combinations were fungicidal and which fungistatic upon plating samples from 5.0 cc. tubes after eight-day incubation. The eight-day results agree with the growth curves, from which it may be seen that the effect of 0.5 minimal inhibitory concentration each of polymyxin B and cycloheximide together is greater than 1.0 minimal inhibitory concentration of either alone.

In Vivo Tests.—An insufficient number of animal experiments have been performed using drugs singly or in combination, both prophylactically and therapeutically, to draw statistically valid conclusions. However, combinations of cycloheximide and polymyxin B are not more toxic than when these drugs are injected individually. Both drugs were injected in a series consisting of two doses a day for three days, except for the prophylactic polymyxin B group, in which mice received 50 mg. per kilogram one hour before being infected; cycloheximide, alone and in combination, was given in 2.5 mg. per kilogram doses, and polymyxin B in 5.0 mg. per kilogram doses. The C. neoformans strain R. H. 1474 is highly virulent, particularly with the number of organisms injected in these experiments, and the infection was considered overwhelming, since both control and treated animals showed no significant difference in average days of survival (Fig. 2).

COMMENT

According to the results of studies of the sensitivity of these drugs to date, cycloheximide and polymyxin B appear to be potentially the most useful against C. neoformans. Blood level concentrations of both can be assayed in man,[16] and there is likewise considerable toxicological data for each drug in humans; in mice, as shown above, the toxicity of the two drugs when used in combination is no greater than when they are used alone, but this data is not available for man. Cases of treatment with cycloheximide alone have been recorded.[17] There have been no published cases of cryptococcic meningitis treated with polymyxin B, although Sweigert [6c] and Eiben [6d] have noted clinical improvement in two unreported cases. The mode of action of each drug would appear to supplement that of the other, as judged by in vitro studies. The theory that organisms surviving in a given drug concentration (in this case, organisms growing out of the end-point tubes for cycloheximide) may be eliminated by another agent, with a different mode of action (such as polymyxin B), might partially explain the synergism already noted and lend further justification to the use of combined therapy in humans.[15a] In support of the observation of the fungistatic action of cycloheximide are the data on cerebrospinal fluid previously reported (Case 1, R. H.[1]), in which the sugars rose and the cultures became negative, only to revert to previous values when intrathecal cycloheximide therapy was terminated. The addition of a fungicidal agent might have eliminated these organisms from the cerebrospinal fluid (although organisms in deeper structures of the neuroaxis could conceivably have remained untouched).

Therapeutic application of the other agents with low minimal inhibitory concentrations (all water insoluble) awaits further data on toxicity in animals and

16. Hellstrom, M.: Assay of Actidione by Paper Disc Method Using Cryptococcus Neoformans, to be published. Stansly, P. G.: A Simple Method for the Assay of Polymyxin in Blood and Urine, Ann. New York Acad. Sc. **51**:980-981, 1949.

17. Carton.[1] Wilson.[2]

humans. It should be noted that although the antimonial compound (Hoffman-LaRoche) has extremely high minimal inhibitory concentration, 1.5 mg. per cubic centimeter, the mouse protection test results are surprisingly good, with repeated treatment of 50 mg. per kilogram reducing mortality from 90% in untreated to 23% in treated animals. In the surviving 77% of the mice very few lesions were found.[18] The results using ethyl vanillate[19] substantiate those of Blank,[5] who found that feasible human dosage produced blood levels sufficient to inhibit Histoplasma but insufficient to inhibit C. neoformans. Agents assayed in vitro because of possible chemical similarity to cycloheximide, e. g., A-2754 (paramethadione, Paradione, Abbott), A-2297 (trimethadione, Tridione, Abbott), Dimedione (Merck), and Mysoline (Ayerst, McKenna, & Harrison) were ineffective against the Cryptococcus.

The pathology of cryptococcic meningitis is somewhat similar to that of tuberculous meningitis, and streptokinase and streptodornase have been used in the latter disease in an attempt to lyse cerebrospinal fluid blocks and thus permit streptomycin to diffuse throughout the full extent of the subarachnoid space.[20] Hyaluronidase may dissolve the polysaccharide capsules of the Cryptococcus, according to some data already in the literature,[21] thus permitting more intimate association of other therapeutic agents with the organism. For these reasons the above-mentioned enzymes were investigated routinely in vitro prior to animal studies now in progress. The possibility of interaction in vitro between the substrate and these enzymes is such that the tube assays cannot be considered significant. However, streptokinase is not antagonistic to either cycloheximide or polymyxin B in vitro. Combinations of antibiotics, as noted, with streptokinase and streptodornase or with hyaluronidase in human therapy would seem to be entirely feasible as far as activity and toxicity are concerned.

SUMMARY

Twenty-nine agents were tested for minimal inhibitory concentration against a standard strain of Cryptococcus neoformans. Of these, cycloheximide (Acti-Dione®), polymyxin B, U-0579, rimocidin, thiolutin, compound 77, and P-968, in the above order, showed inhibition in concentration of 5 γ per cubic centimeter or less. The remainder showed minimal inhibitory concentrations ranging from fairly effective compounds to those without apparent effect.

Studies indicate that cycloheximide is fungistatic; polymyxin B is primarily fungicidal, and U-0579, rimocidin, thiolutin, and compound 77 are fungicidal in their action.

18. Fleming, T. C.: Personal communication to the author.

19. Ethyl vanillate was used clinically on patient R. H. at the Montefiore Hospital, to which she had been transferred for terminal care. Data regarding treatment were obtained from Dr. Arthur E. Gillman, Service of Neurology (Dr. T. J. C. von Storch, Director).

20. Cathie, I. A. B., and MacFarlane, J. C. W.: Adjuvants to Streptomycin in Treating Tuberculous Meningitis in Children, Lancet **2**:784-789, 1950. Williams, S., and Bazeley, P. L.: The Use of Streptokinase in the Treatment of Tuberculous Meningitis, M. J. Australia **2**:690-692, 1950. Knight, V.; Hardy, R. C., and Negrin, J. Jr.: Meningitis Due to Pseudomonas Aeruginosa: Intrathecal Treatment with Streptokinase and Streptodornase and Intramuscular and intrathecal Treatment with Neomycin, J. A. M. A. **149**:1395-1397, 1952.

21. Drouhet, E., and Segretain, G.: Action de l'hyaluronidase sur la capsule de Torula histolytica, Compt. rend. Acad. sc. **228**:424-425, 1949.

Cycloheximide, polymyxin B, compound 77, and streptokinase and streptodornase (Varidase) were tested in dual combinations, in every case showing potentiation of action. Of these, cycloheximide with polymyxin B and cycloheximide with compound 77 were the most potent combinations, both showing a synergistic effect in vitro.

Cryptococci isolated from mice treated with cycloheximide and polymyxin B and organisms from a human case extensively treated with cycloheximide did not develop resistance to these drugs.

Preliminary animal work showed a direct relationship between the size of the inoculum and the average survival rate days. The apparent lack of therapeutic and prophylactic effects of the two agents briefly tested was noted and was partially attributed to the large inoculum and the overwhelming infection thus produced.

Suggestions are made for further therapy of patients with central nervous system cryptococcosis on the basis of these studies.

This work was performed in the Department of Microbiology under a grant from the Department of Neurology (Dr. H. Houston Merritt, Director), College of Physicians and Surgeons, Columbia University. We received constant guidance from Dr. Beatrice C. Seegal and helpful criticism from Dr. Harry M. Rose, Dr. H. Houston Merritt, and Dr. J. Lawrence Pool.

SUCCESSFUL CORTICOTROPIN (ACTH) THERAPY OF WHIPPLE'S DISEASE REFRACTORY TO CORTISONE

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WE REVIEWED in 1950 the 33 cases of lipophagic intestinal granulomatosis published through 1948 and reported an additional one.[1] Aside from its resemblance to the intestinal and mesenteric lipogranulomas, it became obvious during that study that lipophagic intestinal granulomatosis has certain clinical and pathological resemblances to the so-called collagen disorders, such as recurrent polyarthritis, polyserositis, endocardiosis [2] or endocarditis, and histologic evidence of mesenchymal chronic inflammation.[2] This condition also has a broad clinical resemblance to chronic adrenocortical insufficiency, especially in regard to susceptibility to nonspecific stress.

Kampmeier and Peterson,[3] working independently from us, likewise concluded that Whipple's disease properly should be included within the heterogenous entities known as the "rheumatic state." Also, in 1950, the studies of Hendrix and his associates [2] added further impetus to this concept by suggesting a hyperergic factor involved in the pathogenesis, indicating a like thought trend.

Just prior to our last communication, Hench and his group had noted the remarkable remissions obtained through the use of corticotropin (ACTH) and cor-

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1. Plummer, K.; Russi, S.; Harris, W. H., Jr., and Caravati, C. M.: Lipophagic Intestinal Granulomatosis (Whipple's Disease): Clinical and Pathologic Study of 34 Cases, Arch. Int. Med. **86**:280-310 (Aug.) 1950.

2. Hendrix, J. P.; Black-Schaffer, B.; Withers, R. W., and Handler, P.: Whipple's Intestinal Lipodystrophy: Report of 4 Cases, Arch. Int. Med. **85**:91-131 (Jan.) 1950.

3. Kampmeier, R. H., and Peterson, J. C.: Whipple's Disease: Its Relationship to the Rheumatic State, Tr. Am. Clin. & Climatol. A. **61**:248-268 (Oct.) 1949. Peterson, J. C., and Kampmeier, R. H.: Whipple's Intestinal Lipodystrophy: Its Relationship to the Rheumatic State, Am. J. M. Sc. **221**:543-560 (May) 1951.

tisone in various rheumatic disorders.[4] This report was amplified in a later publication.[5]

The observations just mentioned tended to confirm our original proposal that those hormones might exert a favorable effect upon the course of the disease. To date this has been achieved in at least one case reported by Jones [6] and one reported by Janowitz,[7] in which cortisone was used. In the case of Jones and his associates,[6] corticotropin was administered intravenously for 10 days prior to cortisone.

TABLE 1.—*Findings in Reported Cases of Lipophagic Intestinal Granulomatosis, 1949 Through 1952*

Author	Sex	Age, Yr.	Total Duration Until Death or Time of Article, Yr.	Arthritis, Duration Before Last Admission	Gastrointestinal Symptoms *				Weight Loss Prior to Last Admission	Pleurisy	Pericarditis	Respiratory Infections	Melena	Prior Laparotomy	Means of Diagnosis *
					Abdominal Pain	Distention	Constipation	Diarrhea, Duration Before Last Admission, Mo.							
Schutz [8f]	M	35	4.5	4.5	+	+	..	6	+	..	..	..	..	..	P.M.
Janowitz [7]	F	61	2	2	..	..	..	24	+	..	..	..	..	..	Lap.
Kampmeier [3]															
Case 1	M	43	7	7	+	+	+	..	15	..	..	..	+	..	P.M.
Case 2	F	13	4 mo.	3 mo.	+	..	..	..	+	..	..	..	..	..	P.M.
Case 3	M	11	5	..	+	+	..	12+	+	..	..	..	..	..	Lap.
Case 4	M	47	4.5	3+	+	+	..	Few	40	..	..	..	+	+	Lap.
Upton [8a]	M	54	8 mo.	..	+	..	..	7	30	..	..	..	..	..	P.M.
Paulley [8d]	M	56	7	5	+	..	..	6	+	..	..	..	..	..	Lap.
Luton [8c]	M	47	10	10	+	+	..	7	64	..	+	..	..	..	Lap.
Hendrix [2]															
Case 1	M	56	Several	Several	+	+	+	14	90	..	..	+	+	..	Lap. & P.M.
Case 2	M	52	Several or 8 mo.	Several	+	..	..	2	35	..	..	+	+	..	P.M.
Case 3	M	45	5	5	+	+	..	Few	75	..	..	+	..	..	P.M.
Case 4	M	33	15 mo.	15 mo.	+	..	..	15	30	..	..	..	+	..	P.M.
Jones [6]	F	49	2	2	+	+	..	3	25	+	..	..	+	..	Lap.
Russo [8e]															
Case 1	M	45	5	5	+	..	..	24	30	..	..	..	..	..	P.M.
Case 2	M	64	1.5	..	..	..	..	8	40+	..	..	+	..	..	P.M.
Avery Jones [8b]	M	44	5	5	+	..	..	10	+	..	..	..	+	..	P.M.

* The meaning of the abbreviations is as follows: +, present; lap., laparotomy; P.M., post mortem examination.

4. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effect of Hormone of Adrenal Cortex (17 Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotrophic Hormone on Rheumatoid Arthritis, Proc. Staff Meet., Mayo Clin. **24**:181-197 (April 13) 1949. Hench, P. S.; Slocumb, C. H.; Barnes, A. R.; Smith, H. L.; Polley, H. F., and Kendall, E. C.: The Effects of Adrenal Cortical Hormone 17-Hydroxy-11-Dehydrocorticosterone (Compound E) on the Acute Phase of Rheumatic Fever: Preliminary Report, ibid. **24**:277-297 (May 25) 1949.

5. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions: Study in Clinical Physiology, Arch. Int. Med. **85**:545-666 (April) 1950.

6. Jones, C. M.; Benson, J. A.; Rogue, A. Q., and Castleman, B.: Whipple's Disease: The Presentation of a Case with Special Reference to Histochemical Studies of Biopsy Material and Therapeutic Results Following Corticosteroid Therapy, Tr. A. Am. Physicians **65**:276-280, 1952.

7. Janowitz, H. D.; Drachman, S. R.; Wang, Chun, I., and Adlersberg, D.: Observations in a Patient with Lipophagic Intestinal Granulomatosis (Whipple's Disease) Diagnosed During Life, abstract, Progress of the American Gastroenterological Association, May 2, 1952.

TABLE 2.—*Physical Findings in Reported Cases of Lipophagic Intestinal Granulomatosis, 1949 Through 1952*

	Emaciation *	Hypotension	Purpura	Lymphadenopathy	Pigment	Edema	Fever	Abdominal Mass	"Doughy" Abdominal Mass	Glossitis	Tetany	Demonstrable Arthritis	Chylous Ascites	Pleurisy	Pericarditis
Schutz [8f]	+	+	..	+	+	+	+	..	..	..	..	..	..	..	..
Janowitz [7]	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Kampmeier [3]															
Case 1	+	+	..	+	+	+	+	+	..	..	..	..	+	..	+
Case 2	+	..	..	+	+	..	+	+	+	..	..	+	+	..	+
Case 3	+	+	..	..	..	..	..	+	+	..	..	..	+	..	..
Case 4	+	+	+	..	..	+	..	+	+	..	..	..	+	..	..
Upton [8a]	+	+	..	+	+	..	..	+	..	..	..	..	..	..	..
Paulley [8d]	+	+	..	..	+	+	+	..	..	..	..	..	..	..	..
Luton [8c]	+	+	..	+	..	..	+	..	..	..	..	..	+	..	+
Hendrix [2]															
Case 1	+	+	..	..	+	..	..	..	..	+	..	..	..	..	..
Case 2	+	+	..	+	..	..	+	..	..	..	..	..	..	..	..
Case 3	+	+	..	..	..	..	+	..	..	+	..	..	..	..	..
Case 4	+	+	..	..	..	..	+	..	..	..	..	..	..	..	..
Jones [6]	+	..	..	..	+	..	..	..	..	..	..	..	..	..	..
Russo [8e]															
Case 1	+	+	..	+	..	..	..	..	..	..	..	..	..	..	..
Case 2	+	+	..	+	..	+	+	..	..	..	..	..	..	..	..
Avery Jones [8b]	+	+	..	..	+	..	..	..	..	..	..	..	..	..	..

* A plus sign indicates that the condition was present.

TABLE 3.—*Laboratory Findings in Reported Cases of Lipophagic Intestinal Granulomatosis, 1949 Through 1952*

	Secondary Anemia *	Achlorhydria	Increased Fecal Fat	Low Serum Lipids	Low Serum Proteins	Albumin : Globulin Reversal	Hypocalcemia	Low Glucose Tolerance Curve	Low Vitamin A Level (Serum)	Low Vitamin A Tolerance Curve	Low Fecal Nitrogen	X-Ray "Deficiency Pattern"	Low Serum Cholesterol	Eosinophilia	Low 17-Ketosteroids	Albuminuria
Schutz [8f]	+	0	0	+	+	0	+	+	+	..	+	+	+	..	0	..
Janowitz [7]	+	+	..	0	..	..	..	+	+	+	..	..	..	..	..	..
Kampmeier [3]																
Case 1	+	..	..	..	+	0	..	+	..	+	..	..	..	+	..	..
Case 2	+	..	..	..	+	+	..	+	..	+	..	..	..	..	..	..
Case 3	..	..	+	..	+	0	..	0	..	+	..	+	..	+	..	..
Case 4	+	..	..	..	+	..	..	0	..	+	..	..	..	..	..	..
Upton [8a]	+	..	..	..	+	..	..	+	..	..	..	+	+	..	+	+
Paulley [8d]	..	..	+	..	+	..	..	..	..	..	..	+	..	..	..	..
Luton [8c]	..	..	+	..	+	0	0	+	..	..	..	..	+	..	..	..
Hendrix [2]																
Case 1	+	..	+	..	..	+	+	+	..	..	..	+	+	+	..	..
Case 2	+	..	+	..	+	+	+	+	..	..	..	..	..	..	..	+
Case 3	+	+	..	..	..	..	..	..	..	..	..	..	..	..	..	+
Case 4	+	..	..	..	+	0	+	..	..	..	..	+	..	..	..	..
Jones [6]	+	..	..	+	+	0	+	..	..	..	0	+	..	+	+	..
Russo [8e]																
Case 1	+	+	+	..	..	..	..	..	..	..	..	..	..	..	..	+
Case 2	+	..	..	..	0	+	..	..	..	..	..	..	..	..	..	+
Avery Jones [8b]	+	+	+	..	..	..	+	+	..	..	..	..	..	..	..	..

* A plus sign indicates that the condition was present; zero, that it was normal.

The purpose of this report is to further substantiate the concept of lipophagic intestinal granulomatosis as a collagen disorder by recording the response in a new case to corticotropin. The outstanding feature in this case was the ineffectiveness of cortisone therapy over a three-month period, whereas a completely satisfactory remission was obtained later with corticotropin (gel). A possible mechanism for such a response will be discussed later. To our knowledge, this observation has not been previously recorded.

For completeness, reference is made to the case reports published during the period 1949 through 1952,[8] which total 17. Their clinical and laboratory features are noted in Tables 1, 2, and 3.

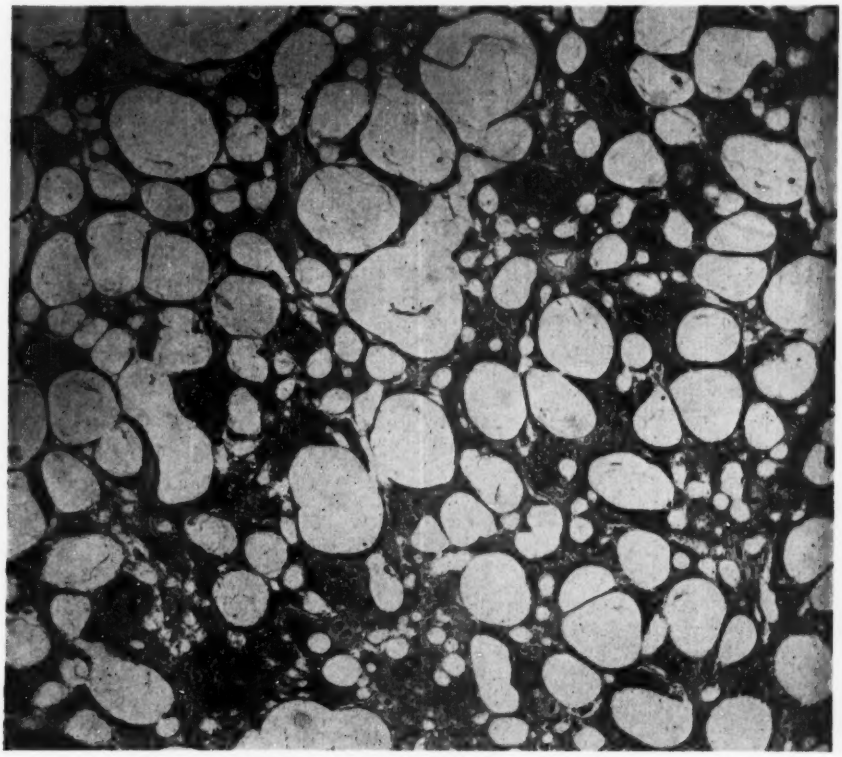

Fig. 1.—Low power photomicrograph showing mesenteric lymph node containing dilated fat-filled sinuses and obliteration of the normal lymphoid architecture by chronic inflammatory reaction.

8. (*a*) Upton, A. C.: Histochemical Investigation of the Mesenchymal Lesions in Whipple's Disease, Am. J. Clin. Path. **22**:755-764 (Aug.) 1952. (*b*) Avery Jones, F., and Paulley, J. W.: Intestinal Lipodystrophy (Whipple's Disease), Lancet **1**:214-216 (Feb. 5) 1949. (*c*) Luton, E. F.: A Possible Cause of Death in Whipple's Disease, Gastroenterology **20**:327-329 (Feb.) 1952. (*d*) Paulley, J. W.: A Case of Whipple's Disease (Intestinal Lipodystrophy), ibid. **22**: 128-133 (Sept.) 1952. (*e*) Russo, F. R.: Whipple's Disease: Review of the Literature and a Report of 2 Cases, A. M. A. Arch. Int. Med. **89**:600-614 (April) 1952. (*f*) Schutz, P. J.; Benner, W. H., and Christian, W. A.: Intestinal Lipodystrophy (Whipple's Disease), Am. J. Med. **7**:553-563 (Oct.) 1949. (*g*) Hendrix.[2] (*h*) Footnote 3. (*i*) Jones.[6] (*j*) Janowitz.[7]

REPORT OF A CASE

A 22-year-old white man was admitted on June 23, 1952, after being recently discharged from the Marine Corps because of disability occasioned by the present illness. The onset of his first symptoms dated back to Dec. 1, 1950, in England, when he had an episode of anorexia, nausea, vomiting, and diarrhea, which was preceded for two weeks by a common cold. A papular eruption over the trunk was also noted. These symptoms subsided gradually over a 10-day period and were followed by a short remission of one week, when he again sought medical aid because of a recurrence, which was identical except for additional signs of pneumonitis and generalized lymphadenopathy. A fleeting polyarthritis then developed, involving the proximal interphalangeal joints and wrist on the right.

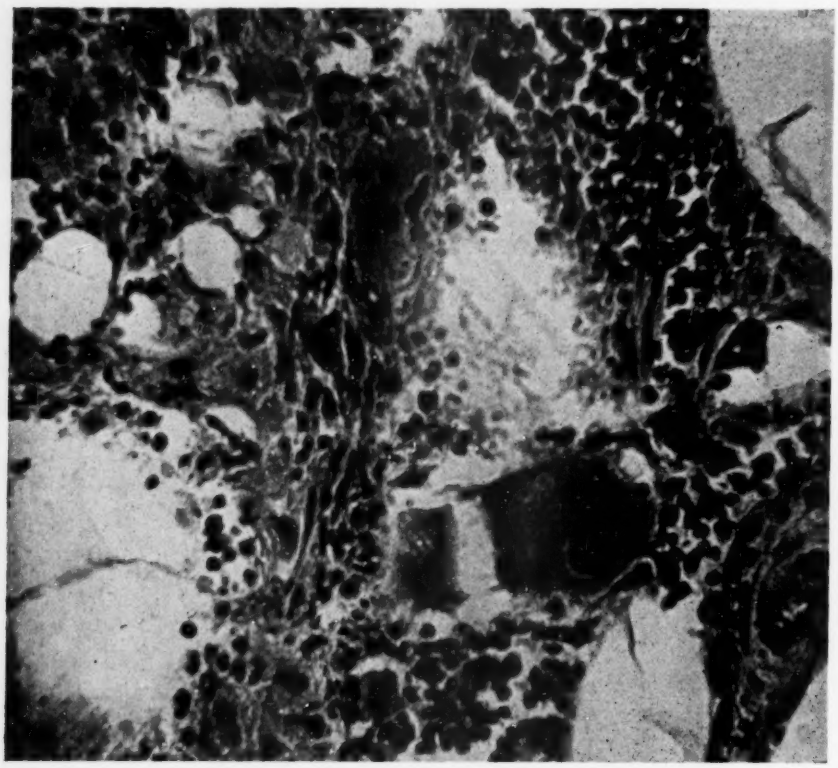

Fig. 2.—High power photomicrograph showing dilated lymph sinuses, foreign body giant cells, and infiltration by large mononuclear cells.

Following a spontaneous recovery there were no further symptoms until November, 1951, when the patient noted tenderness in the left lower quadrant, nausea, vomiting, distention, and a loss of 20 lb. (9 kg.) from his usual weight. An ill-defined mass was palpable in the left lower abdomen. X-ray study after a barium meal and a series of studies of the small bowel provided no pertinent information.

Continuous symptoms necessitated his hospitalization, at the United States Naval Hospital, Camp LeJeune, N. C., in January, 1952. Relevant findings then consisted of marked undernutrition, generalized discrete lymphadenopathy, abdominal tenderness, and a poorly outlined mass in the left lower quadrant. Biopsy of an inguinal lymph node revealed chronic nonspecific lymphadenatis. Sternal marrow showed eosinophilia, myeloid and erythroid hyperplasia, and an increase in plasma cells.

There was no diarrhea, but an average of two poorly formed bulky stools were passed daily. X-ray study after a barium meal then revealed a coarsened mucosal pattern in the duodenum and proximal jejunum, with clumping of barium. One month after admission a large mass occupying the left abdomen became obvious.

In February, 1952, at laparotomy, a large, irregular, firm, and nodular mass was found occupying the major portion of the mesentery of the small bowel. In the retroperitoneal space there were numerous enlarged periaortic lymph nodes. A node removed from the mesenteric chain was grossly and histologically typical of lipophagic intestinal granulomatosis, and this diagnosis was confirmed at the Armed Forces Institute of Pathology (Figs. 1 and 2).

Treatment with cortisone was started March 18, 1952, using 200 mg. for two days and 100 mg. intramuscularly daily thereafter for six weeks, followed by the same dose orally for another six weeks. No improvement was noted, and the patient soon began to have diarrhea consisting of four to eight liquid foul-smelling stools daily. There was progressive deterioration,

TABLE 4.—*Laboratory Data for Patient with Lipophagic Intestinal Granulomatosis*

Tests	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Hemoglobin, gm./100 cc.	9	10	13.5	....	12.5	8.4	12.1	10.1	10.9	....	....	13.1
RBC,* millions cu. mm.	3.7	3.9	....	....	....	3.2	....	....	....	....	....	....
WBC */cu. mm.	5000	9700	8600	....	12500	8000	5600	....	14700	....	....	6900
Sedimentation rate, mm./hr.	....	26	....	....	24	28	....	....	34	....	....	20
Albumin:globulin, gm./100 cc.	....	5.4:1.3	....	....	3.8:3.6	....	3.2:2.4	....	....	3.8:2.7	....	3.9:2.3
Total serum lipids †	....	....	....	....	....	....	11	8	....	18	....	16
Serum sodium, mEq./L.	....	....	....	....	....	....	140	137	141	135	....	....
Serum potassium, mEq./L.	....	....	....	....	....	....	3.0	2.8	4.9	5.1	....	....
Glucose tolerance, mg./100 cc.	....	....	64:75: 94:100: 90	....	....	80:85: 106:106 112:109	....	....	....	Fast. 93	....	Fast. 87
Serum calcium, mg./100 cc.	....	....	9.3	....	....	....	9.0	....	....	9.7	....	10.0
Stool fat/24 hr.	....	....	....	21.6%	....	....	....	....	....	....	....	....
Oxycorticosteroid excretion/ 24 hr., mg.	....	....	....	....	....	....	0.45	....	....	....	....	0.58
Urea nitrogen, blood, mg./100 cc.	....	....	....	....	....	19	....	....	....	....	....	....
Serum cholesterol esters, mg./100 cc.	....	67	....	....	....	....	45	39	....	119	....	80
Serum cholesterol, mg./100 cc.	....	100	....	....	....	....	100	55	....	170	....	152
Inorganic phosphorus, mg./100 cc.	....	....	4.1	....	....	....	....	....	....	....	....	3.9
Absolute eosinophile count	....	....	....	....	....	....	234/ cu. mm.	....	....	160/ cu. mm.	....	144/cu. mm. 69./cu. mm.‡

* RBC = red blood cells; WBC = white blood cells.
† Kunkel Turbidity Units; normal, 16-30 (Kunkel, H. G.; Ahrens, E. H., Jr., and Eisenmenger, W. J.: Gastroenterology, 11: 499 [Oct.] 1948.).
‡ Thorn test.

and narcotics were required for relief of abdominal pain and frequent stools. Cortisone was continued for three months although the clinical course was unaffected during that time.

The patient entered McGuire Veterans Administration Hospital on June 23, 1952. He was rather cachetic, weighing 107 lb. (48 kg.), whereas his previous normal weight had been 145 lb. (65 kg.). The physical findings were as noted previously, with only the addition of a diffuse light-brownish pigmentation, notably over the lower abdomen, and hyperkeratosis over the shoulders and back. X-ray study after a barium meal revealed a "deficiency pattern" as before. Narcotics were required regularly for pain. Bethanechol (Urecholine), 10 mg. four times daily, afforded some relief from abdominal distention.

The laboratory data are recorded in chronological order in Table 4.

In view of the inefficacy of cortisone on a previous adequate trial, corticotropin therapy was started on July 14, 1952, using corticotropin gel, 40 mg. every 12 hours, intramuscularly. Nonspecific improvement slowly occurred in the form of an increased sense of well-being and improved appetite.

Less of narcotics was required, subjective improvement continued, and there was a slight weight gain. One month after corticotropin therapy was begun, dependent edema was noted

and the dose was reduced to 20 mg. The patient was maintained on a high protein, high calorie, low fat diet with supplementary vitamins and potassium chloride. Testosterone was added to enhance positive nitrogen balance.

Abdominal pain continued to be a problem, but was considerably less severe. To alleviate this, an Efocaine [9] splanchnic block was performed on the left side, followed by complete relief to the midabdomen. A subsequent block on the right produced total relief of abdominal pain but was complicated by a slight pleural effusion on the right for several days thereafter. On Sept. 8, 1952, the dose of corticotropin had to be further reduced, to 10 mg., and later to 5 mg. because of edema. Its use was discontinued on Oct. 10, 1952.

Reevaluation of the patient's status on Oct. 28, 1952, confirmed the following progress. He was free of pain, there was no apparent edema, and his appetite was greatly improved. Weight gain had increased steadily from a low of 107 lb. (8 kg.) to 147 lb. (66 kg.) over a four-month period. He had no diarrhea and passed two normally formed stools daily. The abdominal mass and pigmentation had disappeared. There was a noticeable increase in muscle mass and subcutaneous fat. Subjectively the patient felt as well as before the onset of his illness in November,

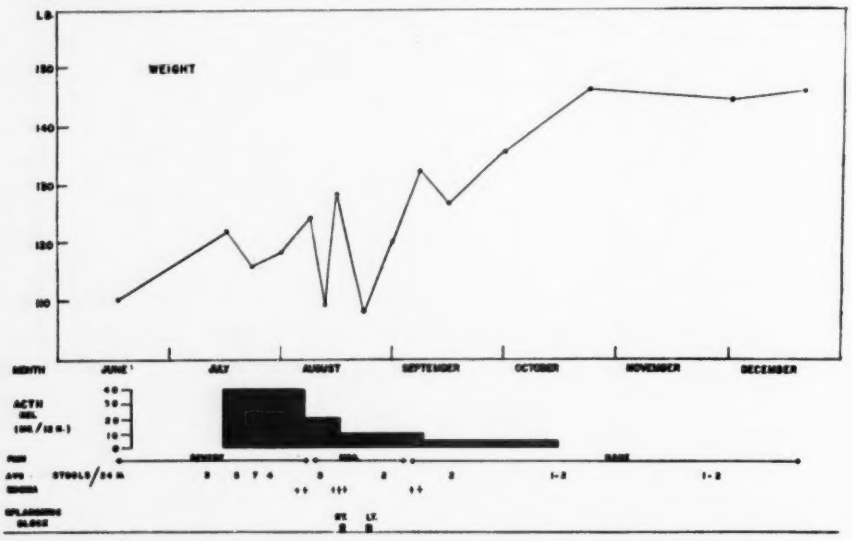

Fig. 3.—Clinical course of the patient during corticotropin (ACTH) therapy.

1950. A short follow-up period of observation on Dec. 18, 1952, showed no change, and there was nothing to indicate an impending or partial relapse. The patient's response to treatment is chronologically shown in Figure 3.

COMMENT

Considering the lack of beneficial response to cortisone in adequate dosage, there is strong indication that corticotropin induced a complete remission in this case. Corticotropin was discontinued four months prior to this report, and absence of a subsequent relapse gives further proof that corticotropin was the factor responsible for the remission, probably by producing adrenocortical hyperplasia.

There are several points in support of this contention: (1) a pronounced weight gain, which at its maximum could not be ascribed to water retention either obvious or occult; (2) diminution in the frequency of stools to normal; (3) relief of pain

9. Efocaine (E. Fougera & Co., Inc.) is a depot solution for local anesthesia.

and distention, which may have been attributable to the Efocaine nerve block initially (6 to 12 days' duration) but whose persistence for such a lengthy period would indicate another mechanism; (4) apparent resolution of the abdominal mass.

If corticotropin has been the effective agent in this case, one might speculate upon the mechanism of action. Basically, it must be predicated upon the induction of a hyperplastic adrenal cortex, with consequent elaboration of other steroids in addition to the 11-dehydro-17-hydroxy type such as cortisone. The general ability of cortisone to promote intestinal absorption as well as its potent action as an inhibitor of inflammatory tissue reaction and antigen-antibody immune responses is established. The remissions achieved by other writers [10] could well be ascribed to these physiologic actions.

However, the failure of cortisone in this instance, coupled with a corticotropin-induced remission, suggests the participation of certain corticosteroids other than that of the 11-dehydro-17 hydroxy configuration. Among these may be mentioned "Compound A" of Kendall (11-dehydrocorticosterone), which has experimentally been shown to enhance fat absorption [11] but whose other physiologic actions are obscure.

It is probable that in this case the constant pain arose from involvement of the afferent splanchnic fibers in the mesentery and retroperitoneum by the granulomatous process. Periodic pain certainly seemed ascribable to marked intestinal stasis and distention. Relief may have been accomplished by a corticotropin-induced, cortisone-like inhibition of granuloma formation about the nerve fibers and a nonspecific promotion of intestinal absorption, thereby reducing distention and stasis. Splanchnic block could also have promoted the latter by removal of sympathetic inhibitory motor impulses temporarily, but interruption of afferent pain fibers was no doubt the major factor in the dramatic relief of pain the first few days thereafter.

As an explanation of the failure of synthetic cortisone alone in this case, it may be postulated that a multisteroid effect is present (including Comopund A), resulting from corticotropin-induced adrenocortical hyperplasia.

To our knowledge thus far this is the first case conclusively shown to be nonresponsive to cortisone yet susceptible to remission from corticotropin administration. A future relapse was expected, since no permanent correction of the underlying pathologic physiology would be achieved through the use of corticotropin. As predicted, this has recently occurred, at the time of this writing. Although the relapse is mild in nature, a renewal of small doses of corticotropin is planned.

SUMMARY

A new case of lipophagic intestinal granulomatosis is reported, in which a remarkable remission has been achieved with corticotropin, whereas an adequate three months' trial of synthetic cortisone therapy was previously ineffective. A mechanism of action of adrenocorticosteroids in this instance is tentatively proposed.

The histologic sections and the clinical and laboratory data pertaining to this case prior to the patient's admittance to our service were provided by the staff of the Medical and Laboratory Services, United States Naval Hospital, United States Marine Base, Camp LeJeune, N. C.

10. Jones.[6] Janowitz.[7]

11. Bergner, G. E.; Lewis, R. A.; Stout, F. W.; Thorn, G. W., and Emerson, K., Jr.: The Effect of 11-Dehydrocorticosterone on Fecal Fat Excretion, abstract, J. Clin. Endocrinol. **8**:606 (July) 1948.

VITAMIN E AND CLIMACTERIC SYNDROME

Failure of Effective Control as Measured by Menopausal Index

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WHILE the value of estrogens in the menopause cannot be denied, there are some clinicians who condemn their use for the climacteric patient. The condemnation is based upon three primary concepts: One is that the entire climacteric syndrome has been designated as one of psychodynamic alterations and can, therefore, be controlled very adequately by psychotherapy or barbiturate sedation.[1] Secondly, evidence of the carcinogenic propensity of estrogens in mice [2] and occasionally in rats has led to the feeling that similar results could be anticipated clinically.[3] The third objection to the use of estrogens in the female climacteric is that in the past a tendency towards uterine bleeding has been noted in patients maintained on estrogen therapy. However, recent moderation of the original recommended doses has diminished the incidence of bleeding noted after such hormone medication.[4] In an attempt to appease those who feel nihilistic toward estrogen therapy, an intensive search has been made to find a therapeutic agent that would be effective in the menopausal patient but at the same time would have little or no estrogenic activity. Thus, there are advocates of phenobarbital and amphetamine therapy as effective nonedocrine methods for the control of the climacteric. Since this type of therapy leaves much to be desired, it was interesting to note the report by Hain and

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1. Hoskins, R. G.: The Psychological Treatment of the Menopause, J. Clin. Endocrinol. **4**:605 (Dec.) 1944.

2. Lacassagne, A.: Apparition de cancers de la mamelle chez la souris mâle, soumise à des injections de folliculine, Compt. rend. Acad. sc. **195**:630 (Oct. 10) 1932. Allen, E., and Gardner, W. U.: Cancer of the Cervix of the Uterus in Hybrid Mice Following Long-Continued Administration of Estrogen, Cancer Res. **1**:359 (May) 1941.

3. Fremont-Smith, M.; Meigs, J. V.; Graham, R. M., and Gilbert, H. H.: Cancer of Endometrium and Prolonged Estrogen Therapy, J. A. M. A. **131**:805 (July 6) 1946.

4. Freed, S. C.: Menstrual Dysfunctions: Climacteric, West. J. Surg. **54**:103 (March) 1946. Jüptner, H.: Excessive Use of Estrogenic Substances During Menopause, Med. Klin. **46**:20 (Jan. 5) 1951. Novak, E., and Novak, E. R.: Textbook of Gynecology, Ed. 4, Baltimore, Williams & Wilkins Company, 1952.

Sym [5] who claimed that vasomotor disturbances of the menopause were effectively reduced in three of four patients by the oral administration of vitamin E (tocopherol). The dose employed by these investigators was in the realm of 6 to 12 mEq. of alpha tocopherol a day. Subsequent to this report, Christy, in this country, observed that the menopausal symptoms and vasomotor instability noted in a group of 25 patients, including both persons with natural and those with surgically induced climacterics, were effectively treated by the administration of alpha tocopherol in doses of 10 to 30 mg. per day.[6] This author believed that her entire group of patients responded to treatment favorably and showed either complete relief or very marked improvement. No untoward or undesirable side-effects were noted. It was also emphasized that in some cases relief of the vasomotor instability was more easily obtained by the use of vitamin E than by the administration of estrogen. It was pointed out in this report that the marked advantage of vitamin E was the effective control of menopausal symptoms without the undesirable effect on secondary sex organs of the female genital system. It was emphasized that vitamin E, because of its lack of estrogenic effect, is the preparation of choice for menopausal patients having coincidental neoplasm and for those with a familial history of carcinoma. In another series of patients, reported by Ferguson in 1948, it was noted that 60 of 66 patients responded favorably to 15 or 30 mg. of alpha tocopherol daily.[7] Occasionally, some of these patients required intramuscular administration of 100 mg. of alpha tocopherol—the so-called stubborn cases. Here, too, the authors commented upon the fact that no objectionable side-effects were noted. In a brief abstract presented by Rubenstein, it was noted that of 17 patients who attained complete relief with estrogens but did not respond to barbiturates or placebos 14 showed adequate improvement when placed on daily administration of 75 mg. of Vitamin E.[8] In only six of these patients, however, was complete relief obtained. The author believed that vitamin E may be useful in the treatment of patients with severe menopausal symptoms in which estrogen may be contraindicated. In a better controlled series of cases, Finkler employed vitamin E therapy in a series of 66 menopausal women. Hormone therapy was contraindicated in 59 of these patients because of malignant, or personal history of neoplastic, disease.[9] Finkler obtained relief in 39 patients by the administration of vitamin E in doses of 20 to 100 mg. of alpha tocopherol per day. In 16 patients the results were only fair, while in 19 no improvement was noted. To check the effect of vitamin E adequately, Finkler gave 17 of the patients who had previously shown a response to vitamin E placebo tablets, and in all these patients recurrences of symptoms were noted within two weeks. While she believed that vitamin E was less effective than estrogen therapy, she noted, however, that it was a valuable adjunct to the menopausal armamentarium, since this prep-

5. Hain, A. M., and Sym, J. C. B.: Control of Menopausal Flushes by Vitamin E, Brit. M. J. **2**:8 (July 3) 1943.

6. Christy, C. J.: Vitamin E in Menopause: Preliminary Report of Experimental and Clinical Study, Am. J. Obst. & Gynec. **50**:84 (July) 1945.

7. Ferguson, H. E.: The Use of Vitamin E in the Menopausal Syndrome, Virginia M. Month. **75**:447 (Sept.) 1948.

8. Rubenstein, B. B.: Vitamin E Diminishes the Vasomotor Symptoms of Menopause, Fed. Proc. **7**:106 (March) 1948.

9. Finkler, R. S.: The Effect of Vitamin E in the Menopause, J. Clin. Endocrinol. **9**:89 (Jan.) 1949.

aration had no noticeable untoward effect and caused no apparent change in the breast or endometrium. Finkler reemphasized the fact that vitamin E may be the preparation of choice for those patients with a personal or familial history of carcinoma.

In contrast to the reports that have just been discussed, a later report by McLaren in the *British Medical Journal* showed that he was able to obtain adequate relief in 64% of his patients when he administered doses in the realm of 500 mg. per day for 37 days.[10] He found that the patients who were treatment failures did not respond to prolonged or heavy doses but that they could be quickly relieved by diethylstilbestrol. The advantages of vitamin E as reported by this author were that the preparation was not an estrogen and produces no sudden change in the clinical appearance of the lower genital tract. He did, however, remark that prolonged and heavy dosage caused healing in 50% of the patients with senile vaginitis. The editorial comment made in the same journal issue was that vitamin E may be prescribed in cases of menopausal flushes when the administration of estrogen is contraindicated.[11] The value of its use in other clinical conditions except for Dupuytren's contractures, however, was questioned. Perloff, in an extensive paper on therapy of the menopause, noted that doses of 75 to 150 mg. daily of tocopherol completely relieved symptoms in 26.1% of treated patients, while another 26% were improved.[12] He noted, however, that the relatively high cost of the material and the unpredictability of response made the compound economically unsound. Kavinoky, in an extensive series of patients, found vitamin E therapy to be worthy of merit.[13] However, it must be noted that increasing the dosage from 10 to 25 mg. up to 100 mg. daily was not accompanied by a concomitant increase in effectiveness of therapy. Sixty-two per cent of the patients' symptoms were controlled with 10 to 25 mg. of alpha tocopherol per day as compared to 60% effectiveness at the 50 mg. dose level and 75% effectiveness on 100 mg. of alpha tocopherol per day.

Other reports in the literature on the effectiveness of vitamin E in the menopause may be summarized by the statement that they all indicate the value of vitamin E but fail to include adequate control data on placebo therapy.[14] It is of interest, nevertheless, to note that Shute, a strong advocate of the use of vitamin E in medicine, claimed that 30 to 75 mg. of alpha tocopherol a day was not as

10. McLaren, H. C.: Vitamin E in the Menopause, Brit. M. J. **2**:1378 (Dec. 17) 1949.

11. Vitamin E Therapy, Editorial, Brit. M. J. **2**:1399 (Dec. 17) 1949.

12. Perloff, W. H.: Treatment of the Menopause, Am. J. Obst. & Gynec. **58**:684 (Oct.) 1949.

13. Kavinoky, N. R.: Vitamin E and the Control of Climacteric Symptoms: Report of Results in 171 Women, Ann. West. Med. & Surg. **4**:27 (Jan.) 1950.

14. Cuatrecasas, J.: Action of Tocopherols on Neurovegetative Syndromes, Semana méd. **2**:146 (July 22) 1948. Cummings, H. H.: Climacteric and Its Management, J. Michigan M. Soc. **47**:1373 (Dec.) 1948. Pollosson, E.; Haour, P., and Blanc: On the Effect of Testosterone and Its Association with Vitamin E in the Menopause, Bull. Assoc. gynec. et obst. **2**:225, 1950. Brax, J., and Caldas, V.: Effect of Estrogens and Vitamin E on the Menopausal Syndrome, Rev. clín. Inst. maternal **3**:63 (Jan.) 1951. Harris, P. L.: Vitamin E, Its Role in the Menopause, J. Am. Osteopath. A. **50**:586 (July) 1951. Pescetto, G.: Vitamin E and Climacteric Disorders, Arch. "E. Maragliano" pat. e clin. **6**:325 (March-April) 1951. Sanchez-Ibañez, J. M.: Treatment of Hot Flashes of the Climacteric with Vitamin E, Rev. españ. obst. y ginec. **8**:247, 1951. Sikkema, S. H.: Menopausal Syndrome Treated with Alpha-Tocopherol: Report of 2 Cases and Review of the Literature, Rocky Mountain M. J. **48**:505 (July) 1951.

effective as estrogen in controlling the intensity and frequency of hot flushes of the menopause.[15]

On the basis of the apparent clinical effectiveness of vitamin E in the menopause, as presented in the literature, we thought it would be advisable to reevaluate the effectiveness of alpha tocopherol therapy in the female climacteric by means of the menopausal index. The menopausal index has been utilized as a method of comparative evaluation of different estrogenic and nonestrogenic preparations in the climacteric patient.[16] While the methodology of the menopausal index has been described in previous reports, it might be worth while to note that this index represents a numerical conversion of the severity of the 11 most common menopausal symptoms. The symptoms evaluated are presented in Table 1, and their numerical conversion is based upon previously described technics. The computation of the menopausal index for an arbitrary case is presented for clarity (Table 1). We have changed the menopausal index discussed in our first paper,

TABLE 1.—*Menopausal Index*

Symptoms	Factor	Severity *	Numerical Conversion
1. Vasomotor	4	+ = 3	12
2. Paresthesia	2	+ = 3	6
3. Insomnia	2	+ = 3	6
4. Nervousness	2	S = 1	2
5. Melancholia	1	O = 0	0
6. Vertigo	1	O = 0	0
7. Weakness (fatigue)	1	M = 2	2
8. Arthralgia and myalgia	1	S = 1	1
9. Headaches	1	+ = 3	3
10. Palpitation	1	M = 2	2
11. Formication	1	S = 1	1
Menopausal index (sum)			35

* Meanings of the abbreviations are as follows: O = None = 0; M = Moderate = 2; Slight = 1; + = Marked = 3.

on estradiol pellet implantation in the surgical menopause,[16b] in one respect, in that weighted importance is given to the first four symptoms—namely, vasomotor symptoms, nervousness, insomnia, and paresthesia. These are given increased weight in compiling the menopausal index since we believe that they are the most important symptoms comprising the menopausal syndrome and are responsible in great part for the patient's presenting herself for therapy. The methods used in the main portion of this study also include the so-called blind testing technic, whereby the interrogator and the patient are not aware of the preparation that was administered. In so doing and by using this method of investigation we feel that the subjective impressions of the investigator or the patient can be nullified.

15. Shute, E. V.: Vitamin E for Menopausal Complaints, Summary **2**:34 (Jan.) 1950.

16. (*a*) Kupperman, H. S.; Blatt, M. H. G.; Wiesbader, H., and Togashi, S.: Use of the Amenorrhea and Menopausal Index in the Clinical Evaluation of Estrogenic Compounds, Fed. Proc. **11**:365 (March) 1952. (*b*) Delaplaine, R. W.; Bottomy, J. R.; Blatt, M.; Wiesbader, H., and Kupperman, H. S.: Effective Control of the Surgical Menopause by Estradiol Pellet Implantation at the Time of Surgery, Surg., Gynec. & Obst. **94**:323 (March) 1952. (*c*) Kupperman, H. S.; Blatt, M. H. G.; Wiesbader, H., and Togashi, S.: Comparative Clinical Evaluation of Estrogenic Preparations by the Menopausal and Amenorrhea Indices, J. Clin. Endocrinol. to be published.

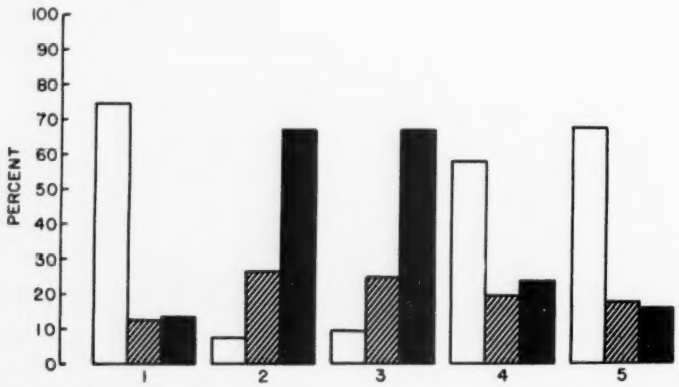
The menopausal index data also permit a statistical comparison between the various compounds that were employed.

The present study is based upon a comparison of the effect of vitamin E[17] upon the patient response as compared to two standard estrogens, ethinyl estradiol[18] and conjugated estrogenic substances (equine).[19] In addition to these two estrogens, phenobarbital and placebos were used liberally throughout the study, which covered three years.

TABLE 2.—*Effect of Vitamin E on Menopausal Symptoms*

Compound	Daily Dose	Patients, No.	Response: Poor, Patients, No.	Poor, %	Moderate, Patients, No.	Moderate, %	Excellent, Patients, No.	Excellent, %
Vitamin E	50-100 mg.	82	61	74.4	10	12.2	11	13.4
Ethinyl estradiol	0.05 mg.	107	8	7.4	28	26.1	71	66.5
Conjugated estrogens (equine)	1.25 mg.	173	16	9.2	42	24.3	115	66.5
Phenobarbital	15 mg. T.I.D.*	88	50	57.2	17	19.2	21	23.6
Placebo	1 tablet	298	199	67.0	52	17.4	47	15.6

* T.I.D. = Three times a day.



Effect of vitamin E on menopausal symptoms: *1*, vitamin E; *2*, ethinyl estradiol; *3*, estrogenic substances; *4*, phenobarbital; *5*, placebo. The white bars indicate poor response; hatched bars, moderate response, and black bars, excellent response.

The complete analysis of the cases studied is presented in Table 2. The chart is a graphic presentation of the relative effectiveness of the different compounds. From the data and from the Chart we see that ethinyl estradiol and conjugated estrogenic substances are comparable in their effectiveness. On the other hand, vitamin E was found to be much less effective than either one of these

17. Kindly supplied as alpha tocopherol acetate in the form of E-sorb by Mr. Leo Schultenover of Wyeth, Inc., and as Ephynal acetate by Dr. Elmer Severinghaus of Hoffman-LaRoche, Inc.

18. Furnished as Estinyl through the courtesy of Dr. Norman Hemingway of the Schering Corporation.

19. Kindly supplied as Premarin by Dr. Stan Jaros of Ayerst, McKenna & Harrison, Ltd. and as Conestron by Mr. Leo Schultenover of Wyeth, Inc.

two estrogens. Approximately 75% of the patients on vitamin E failed to show a satisfactory response, in contrast to 25% that showed a moderate to excellent response. This is comparable to the results attained with placebos, in which it was noted that approximately 67% of the patients on placebos failed to show an adequate response, while 33% of those patients reported satisfactory results. Phenobarbital was more effective than either placebo or vitamin E therapy. The use of this barbiturate proved to be ineffective in 57% of the patients, while 43% showed an adequate therapeutic response. On the basis of our data, we feel that vitamin E is no more effective than a placebo and is certainly less effective than phenobarbital in controlling the menopausal symptoms of most of the patients in the endocrine clinic at Bellevue Hospital.

COMMENT

While it would be of inestimable value to have a preparation such as vitamin E for the adequate control of menopausal symptoms, we fail to see that it achieves any greater effect than that observed with placebo therapy alone. We are at a loss to explain the inconsistency between our results and those of other investigators that were reviewed above; we feel, however, that perhaps the method of investigation is responsible in part for these discrepancies. Only by the objective evaluation of different estrogenic preparations can one remove the subjective bias of the investigator at the time of the interrogation of the patient.[16a, c] In addition, we believe that the menopausal index, as a statistical tool, is of great value in comparing the effectiveness of the different estrogenic preparations.[16c] The method also lends itself admirably well to a statistical comparison of results of therapy with the different estrogens. The support for this statement has been discussed more extensively in a previous report, in which we see that a comparison of the activity of different estrogenic preparations by the menopausal and the amenorrhea index gave exceedingly uniform results.[16c] The amenorrhea index is based more upon concrete facts and less upon subjectiveness of the patient. Comparable results obtained with an objective test such as the amenorrhea index and a subjective test, the menopausal index, establishes the validity of the latter. The menopausal index when properly employed with a sufficient number of patients actually provides a technique for human assay of estrogenic or nonestrogenic preparations.

In trying to relate our observations to those of other investigators, one should note that the previous reports that have been cited have been based primarily upon the effect of vitamin E on vasomotor symptoms alone. While the vasomotor symptoms are predominant as an early manifestation of the menopause, we do not believe that they are the only symptoms that the patient should be treated for or with which the physician should be concerned. The differences between the lack of effectiveness of vitamin E that we note in our report and the therapeutic activity noted by the other investigators are based upon the fact that we took into consideration the other symptoms noted in the climacteric, which are so prevalent and frequently observed in the menopausal patient. However, by the increased importance that we give vasomotor symptoms through the use of the weighted factor, one should tend to obtain standardized results under any system of classification. If vasomotor symptoms were adequately controlled by vitamin E in our patients, the therapeutic effect of this preparation would show up very markedly

in the calculated menopausal index, since vasomotor symptoms are given a weighted factor of four. The severity of the vasomotor symptoms is thereby multiplied by four, thus giving these complaints far greater emphasis and importance in the final compilation of the menopausal index than the other symptoms that are recorded.

Consideration of the mechanism of action of vitamin E is also obscure. Estrogen therapy must be considered as replacement therapy. Certainly the same cannot be said for vitamin E. Except for McLaren, who used massive doses of 500 mg. per day, as reported in his paper, it is felt by most people that vitamin E by itself does not have any estrogenic effect in either rats or humans.[19] One possible mechanism that may conceivably explain the activity of vitamin E in the human pertains to progesterone metabolism. It has been demonstrated that vitamin E may cause some changes in the intermediary metabolism of this steroid.[20] This, nevertheless, does not explain the mechanism of action of vitamin E in the menopause. Vitamin E has not been shown to play a role in the intermediary metabolism of estrogen. Unpublished observations[21] that we have in our laboratory have shown that the parenteral administration to rats of vitamin E in the form of disodium tocopherol phosphate was entirely without effect upon the gonadotrophic activity of the anterior pituitary. The pituitary glands of castrate rats treated with disodium tocopherol phosphate, together with glands from castrate controls, were assayed in immature female rats. The gonadotrophic potency of the hypophysis from the two groups of castrate rats was identical, indicating that disodium tocopherol phosphate did not alter the gonadotrophic content of the castrate rat pituitary. Vitamin E was also without effect in decreasing the gonadotrophic hypersecretion from the pituitary glands of castrate rats. This was manifested by the injection of alpha tocopherol solution into the castrate partner of parabiotic rats. Disodium tocopherol phosphate failed to inhibit the gonadotrophic secretion of the castrate pituitary. Such inhibition is readily demonstrated by minute doses of parenteral estrogens in such an experimental setup.[22] Vitamin E in these series of experiments failed to show any evidence of pituitary inhibition or any evidence of estrogenic activity, as manifested by end-organ response. The failure of demonstration of a concrete physiologic effect of alpha tocopherol in animals and its obscure role in the absence of vitamin E deficiency would also raise serious doubts as to its effectiveness in the menopause.

Finally, we must consider on the basis of our data and the data of others, reported in the literature, that a placebo would be effective in approximately 30% of all patients. The beneficial effect of vitamin E must be considered as being in the same range of effectiveness as a placebo. The activity of a placebo can be explained if we consider the pharmacology of a placebo.[23] The administration of any medicament to the entire organism can induce certain changes in reaction of the organism and thereby relieve subjective findings. However, for

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20. de Watteville, H.; Borth, R., and Gsell, M.: Effect of Dl-Alpha-Tocopherol Acetate on Progesterone Metabolism, J. Clin. Endocrinol. **8**:982 (Nov.) 1948.

21. Kupperman, H. S.: Unpublished data.

22. Footnote deleted.

23. Wolf, S.: Effects of Suggestion and Conditioning on the Action of Chemical Agents in Human Subjects—The Pharmacology of Placebos, J. Clin. Invest. **29**:100 (Jan.) 1950.

a drug to be considered effective in such diseases or symptom complexes it must achieve a significant improvement over the placebo drug; i. e., in the menopausal patient an increased incidence in improvement for a significant response to a therapeutic agent must be noted over the 30% effectiveness of placebo therapy. Results attributed to placebo response may be noted in Perloff's paper, in which a satisfactory effect was observed in only 52% of the patients treated with vitamin E.[12] In addition, the great variability of dose employed, ranging from 10 to 500 mg. of alpha tocopherol a day, was not associated with increase in the therapeutic effectiveness of the drug.[24] This also lends credence to the premise that vitamin E actually assumes no greater effect than that obtained with a placebo.

SUMMARY AND CONCLUSIONS

The comparative effectiveness of vitamin E, ethinyl estradiol, conjugated estrogenic substances (equine), phenobarbital, and placebos in the female climacteric was studied by the blind testing technic, utilizing the menopausal index as the criterion of evaluation.

This methodology provided an unbiased and statistical means of study. The results of the investigation showed that vitamin E administered in the form of 50 to 100 mg. of alpha tocopherol acetate a day was no more active than a placebo in the control of menopausal symptoms and proved to be effective in only 25.6% of 82 patients treated.

Placebo therapy provided adequate results in 33% of 298 patients treated. Phenobarbital was therapeutically successful in 42.8% of 88 climacteric patients. (Both ethinyl estradiol, 0.05 mg. a day, and conjugated estrogenic substances (equine), 1.25 mg. a day, were comparable in activity and adequately controlled menopausal symptoms in 92.6% and 90.8% of 107 and 173 patients, respectively).

The failure of vitamin E to exhibit therapeutic value in this study is in line with its apparent lack of pharmacologic activity experimentally in the absence of vitamin E deficiency. Its purported value in the menopause must be ascribed to its placebo-like effect.

24. Hain.[5] Christy.[6] McLaren.[10] Kavinoky.[13]

Case Reports

SUPERIOR VENA CAVA SYNDROME

Differentiation Between Simple Obstruction and Aorticocaval Communication

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RECENTLY we observed a case of superior vena cava syndrome which resulted from a dissecting aneurysm of the thoracic aorta. This unusual combination of vascular lesions prompted us to review the autopsy files of the Rhode Island Hospital. In the period 1932-1951, a total of 7,006 autopsies were performed. Dissecting aneurysm of the aorta was encountered in 25 cases, an incidence of 0.35%. In none of these was there superior vena cava obstruction. A review of the literature disclosed that in only one other instance has such an entity been described.[1] We wish to report the second such case, which clearly demonstrated simple obstruction of the superior vena cava. In addition, we wish to present one of two cases of aorticocaval communication treated at the Rhode Island Hospital and to differentiate between this condition and simple obstruction of the superior vena cava.

REPORT OF CASES

CASE 1.—E. M., a 41-year-old white man, was admitted to the Rhode Island Hospital on Nov. 6, 1952, because of extreme cyanosis involving the head, arms, and upper part of the chest. Two days prior to admission, while walking down a flight of stairs at his home, he experienced sudden severe substernal pain radiating down the middle of the body to the level of the umbilicus. This episode was followed by syncope. The patient was carried back upstairs and shortly afterwards was admitted to the psychiatric ward of the Charles V. Chapin Hospital, because it was thought that he was suffering from alcoholism. At that institution a presumptive diagnosis of superior vena cava obstruction was made, and the patient was transferred to the Rhode Island Hospital for further care.

Past History.—The patient was studied at the Lahey Clinic in 1946 because of a neurological disorder. It was thought at that time that he probably had widespread disseminated sclerosis.

Physical Examination.—The temperature was 100.8 F., pulse rate 120, respiration 28, blood pressure 125/96 (left arm) and 130/90 (right arm). The patient was a well-developed well-nourished man lying quietly in bed in moderate respiratory distress. The skin was a striking reddish-blue in both upper extremities and the neck, chest, head, and face. The veins of the neck and arms were obviously engorged. The skin was edematous in the upper portions of the body. No rash or ulcers were noted. The lips were cyanotic. The conjunctivae were slightly injected. The pupils were round, regular, and equal and reacted to light and accommodation. The fundi revealed normal discs with no hemorrhages or exudates. The tongue was dry and well papillated. The carotid pulsations in the neck were easily palpable. The lungs were clear to auscultation and percussion. No widening of the mediastinum could be demonstrated by percussion. The heart was normal in size, with normal sinus rhythm. No murmur or thrill could be detected on careful examination of the right anterior chest, sternum, and precordium.

From the Departments of Medicine and Cardiology, Rhode Island Hospital.

1. Baker, L. A.: Dissecting Aneurysm of the Aorta with Complete Obstruction of the Superior Vena Cava, M. Bull. Vet. Admin. **17**:170 (Oct.) 1940.

The sounds at the base were somewhat difficult to hear. No abdominal masses or organs were palpable. There were pronation and inversion of the right foot, with moderate contraction of the extensor tendons of the toes of the left foot. Pulsations were felt in both radial and femoral arteries and they were bilaterally equal in intensity. Neurological examination revealed the absence of both ankle and knee jerks. Bilateral plantar extensor responses were present. There was flaccidity of the right arm and leg. The finer movements of the left hand were partially lost. There were no signs of cranial nerve involvement.

Laboratory Findings.—Hemoglobin was 12.3 gm., red blood cell count 3,910,000, and white blood cell count 19,950, with 78% polymorphonuclear leucocytes. Blood urea nitrogen was 24 mg. per 100 cc., prothrombin activity 86%, Hinton blood test negative, and venous pressure 240 mm. (right arm); no oscillation of the manometer column was noted. Circulation time, arm to tongue, was 55 seconds with sodium dehydrocholate (Decholin sodium). Chest fluoroscopy revealed a prominent bulge in the region of the ascending aorta, which pulsated synchronously with cardiac systole. The heart appeared slightly enlarged to the left, and had a transverse

Fig. 1 (Case 1; E. M.).—Dusky cyanosis of the upper portion of the arms, trunk, and face.

diameter of 15 cm. as compared to the intrathoracic diameter of 26.5 cm. An electrocardiogram was within normal limits.

Course.—It was felt that there was obstruction of the superior vena cava, probably secondary to an aneurysm of the thoracic aorta. Treatment consisted of nasal oxygen and sedation. The patient's course was downhill, and on the third hospital day he suddenly died.

Postmortem Findings.—The diagnosis at necropsy was saccular aneurysm of the ascending arch of the aorta with rupture and hematopericardium; there was dissecting aneurysm of the entire aorta, great vessels of the arch, and left renal and common iliac arteries, and thrombosis of the superior vena cava. Gross organ diagnosis of the heart showed hematopericardium, coronary arteriosclerosis Grade 2, and moderate compression of the right atrium by aortic aneurysm. In the lungs there was an infarct in the lower right lobe and partial atelectasis in both lower lobes. Inspection of the vessels showed saccular aneurysm of the entire aorta, with dissection along the innominate, left carotid, left subclavian, left renal, and both common iliac arteries. There were compression and thrombosis of the superior vena cava.

Case 2.—H. L., a 51-year-old white married man, was admitted to the Rhode Island Hospital on June 29, 1952, because of chest pain and of swelling and cyanosis of the face, neck, and upper chest of about four hours' duration. The patient had been confined to the Butler Hospital for the

past 10 years because of paresis and syphilitic meningoencephalitis. A diagnosis of syphilitic aneurysm was made at that institution. Lately the patient had been allowed to perform small jobs around the hospital. On the morning of admission, while working in the greenhouse, he

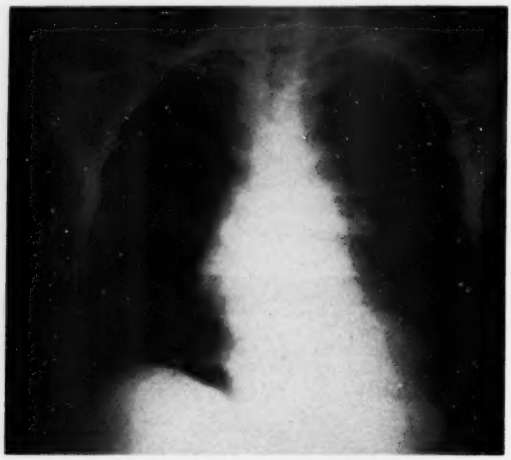

Fig. 2 (Case 1; E. M.).—X-ray of chest showing widening of the mediastinum.

Fig. 3 (Case 2; H. L.).—X-ray of chest showing aneurysm of the ascending and descending aorta.

began to complain of vague pains in his chest and substernal area, which became quite intense within a short period of time. A bluish color appeared in the upper portion of his body, and he became progressively more short of breath. He was transferred immediately to the Rhode Island Hospital.

Physical Examination.—The temperature was 96.4 F., pulse rate 100, respiration 30, and blood pressure 110/30 (left arm) and 105/30 (right arm).

The patient was a well-developed well-nourished muscular man who appeared to be in moderate respiratory distress. There were marked swelling and cyanosis of the neck and face. The patient could not speak coherently. The pupils were pin-point and did not react to light. The conjunctivae and corneae were injected with early chemosis. The fundi could not be visualized. There were edema and cyanosis of the nasal and buccal mucosa as well as of the uvula and pharynx. The neck veins were engorged and pulsated. The trachea was in the midline. There were cyanosis and an increased venous pattern over the upper third of the chest anteriorly and posteriorly, with a good deal of tissue swelling. The mediastinum was widened to percussion. The heart was enlarged to the left of the midclavicular line. There was a normal sinus rhythm. A machinery type of murmur occupying both phases of the cardiac cycle was

Fig. 4.—Front view of the heart and great vessels showing the saccular aneurysm of the ascending arch with rupture and dissection of the aorta.

heard in the third and fourth right interspaces, just to the right of the sternum. A thrill was felt in this region. No masses were felt in the abdomen. Peripheral pulses were felt, as were the arterial pulsations in the neck. Both arms were edematous. Reflexes were absent in the knees and ankles.

Laboratory Findings.—A chest x-ray made with portable apparatus showed a large aneurysm of the ascending and transverse aorta. The aneurysm of the ascending aorta was about 9 cm. in length and extended toward the right about 6 cm. There was linear calcification in its walls.

Course.—It was felt that this patient had an occlusion of the superior vena cava secondary to aorticocaval communication. The patient's condition became steadily worse; he was put in oxygen and given sedatives. His dyspnea became pronounced, and the edema, cyanosis, and venous pattern extended down to the costal margin. In a final attempt to delay the inevitable outcome, a cephalofemoral vein anastomosis was done externally by cutting down on the femoral

and cephalic veins, inserting a plastic cannula in each, and connecting the cannulas with a rubber tube. The tube was filled with heparin and saline and a continuous drip of heparin and saline (100 mg. per liter) was infused into the rubber tube to prevent clotting. The anastomosis functioned well at first, but gradually the flow of blood from the cephalic to the femoral vein diminished. Laryngeal stridor developed and the patient died on the same day.

Postmortem Findings.—The diagnosis at necropsy was aneurysm of the ascending and descending aorta, with rupture into the superior vena cava. Gross organ diagnosis showed compression atelectasis of part of the upper right lobe of the lung. The pericardium showed edema. The heart weighed 315 gm.; measurements of the tricuspid, pulmonary, and mitral valves were

Fig. 5.—Dissecting aneurysm (end on view) of the aorta. Arrows to the left point to the aortic lumen compressed by a hematoma within its wall. Arrow on the right indicates the thrombosed superior vena cava.

13 mm., 7 mm., and 10 mm., respectively; all the cusps were flexible and delicate. They were free of plaques. The commissures were discrete. The myocardium of the right ventricle measured 0.2 cm. in thickness; the myocardium of the left ventricle measured 1.1 cm. in thickness. The coronary arteries were free of marked atherosclerosis. There was a linear streak of fibrosis in the lateral wall of the left ventricle. There was a rounded aneurysm of the ascending aorta and of the descending aorta. The latter had eroded the fourth and fifth vertebrae. Commencing immediately above the aortic valve there was marked arteriosclerosis. The superior vena cava was compressed between the aneurysm of the ascending aorta and the upper right lobe of the lung. A fistula between the aneurysm and the superior vena cava could be demonstrated.

COMMENT

Obstruction of the superior vena cava from any cause may still be considered a rarity. This syndrome was first described in 1752 by Hunter.[2] Fischer, in 1904,[3] was able to collect 252 cases, and by 1946 [4] 250 additional cases were published in the world literature. Since that time approximately 55 cases [5] have been reported. In addition, 10 cases have been studied at the Rhode Island Hospital, bringing the total to date to 567.

2. Hunter, W.: History of Aneurysm of the Aorta with Some Remarks on Aneurysms in General, Med. Observations & Inquiries **1**:323, 1757.

3. Fischer, J.: Über Verengrung und Verschliessung der Vena cava superior, Inaugural Dissertation, Halle, Wischau and Burkhardt, Germany, 1904; cited by F. T. McIntire and E. M. Sykes, Jr.

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Aortic aneurysm is the cause of approximately 35% of cases of superior vena cava obstruction, and an equal number result from mediastinal tumor, either primary or metastatic. A third causative group is found in the chronic inflammatory diseases involving the mediastinum. Aortic aneurysm is prone to rupture, and perforation may occur into the superior vena cava producing aorticocaval communication. This syndrome was first described by Beevor in 1832,[6] and in 1880 Pepper and Griffith [7] laid down the diagnostic criteria, which are still classic. Sirota,[5m] in 1950, reviewed the literature and stated that the total number of cases reported was 110.

Superior vena cava syndrome may have a sudden and dramatic onset or it may develop insidiously. In any case with an acute onset one should attempt to distinguish between simple obstruction of this great vein and obstruction secondary to perforation of an aortic aneurysm into the superior vena cava, resulting in aorticocaval fistula. Both are characterized by the sudden appearance of cyanosis and edema of the face, neck, and upper extremities. Distended veins appear in these

Superior Vena Cava Syndrome—Differentiation Between Simple Obstruction and Aorticocaval Communication

	Simple Obstruction	Aorticocaval Communication
Murmur	Absent	To and fro; 3rd-4th intercostal space to right sternum Present (62%)
Thrill	Absent	Present (23%)
Corrigan's pulse	Absent	Present (50%)
Pulsating veins	Absent	Present (100%)
Venous pressure	Elevated	Elevated, but with systolic thrust of column manometer
Pulse pressure	Normal	Wide (50%)
Dyspnea and orthopnea	Present (75%)	Present (75%)
Cyanosis	Gradual onset	Sudden onset
Edema	Characteristic	Characteristic
Mental symptoms	Common	Common
Electrocardiogram	No specific pattern	Right ventricular strain common
Immediate prognosis	Fair	Poor

areas. The venous pressure becomes elevated. Dyspnea, orthopnea, and cerebral symptoms are common to both. However, in the presence of a communication between the aorta and the vena cava certain other signs appear, which are diagnostic of aorticocaval fistula. 1. There is a machinery murmur in the third right interspace. This is one of the most characteristic signs and was present in 62.5% of 81 cases analyzed by Alex.[8] 2. A systolic thrill may be felt in approximately 25% of cases. 3. When the venous pressure is measured, the column in the manometer will oscillate with each systolic thrust. 4. Signs of anteriovenous aneurysm, such as Corrigan's pulse, capillary and hepatic pulsations, and Duroziez' murmur will appear.

The differentiation of these two types of obstruction of the superior vena cava may have some clinical importance. With the rapid strides that are being made in

6. Beevor: Case Reported Before Middlesex Medical Society, Lancet **1**:800; **2**:63, 1832-1833.

7. Pepper, W., and Griffith, J. P. C.: Varicose Aneurisms of Aorta and Superior Vena Cava, Am. J. M. Sc. **100**:329, 1890.

8. Alex, M.: Rupture of Aortic Aneurysm into the Superior Vena Cava, Am. Heart J. **39**:455 (March) 1950.

cardiac surgery,[9] it may be of value to know whether one is dealing with an aorticocaval fistula. Likewise, the usual forms of therapy employed in simple obstruction of the superior vena cava have no place in the management of arteriovenous aneurysm in the thorax. Prognosis is much better in the absence of a communication between those great vessels, unless the simple obstruction is the result of a dissecting aneurysm in the thorax, as in Case 1.

The first case presented is of unusual interest because of its rarity. We feel that the antemortem diagnosis of a dissecting aneurysm should have been considered, because of the sudden onset of severe substernal pain with radiation to the abdomen. Pain resulting from aorticocaval fistulae is usually choking or squeezing in nature and does not radiate to the abdomen. We wish to emphasize that the presence of this type of pain pattern in a patient with superior vena cava obstruction should make one strongly consider the possibility of dissecting aneurysm of the thoracic aorta.

SUMMARY

A differentiation between simple obstruction of the superior vena cava and aorticocaval communication is made.

The second case in the world literature of superior vena cava syndrome secondary to a dissecting aneurysm of the thoracic aorta is reported.

The presence of chest pain radiating to the abdomen in a patient with superior vena cava syndrome should make one consider the diagnosis of dissecting aneurysm of the thoracic aorta.

9. Stokes, T. L., and Gibbon, J. H., Jr.: Experimental Maintenance of Life by Mechanical Heart and Lung During Occlusion of Venae Cavae Followed by Survival, Surg., Gynec. & Obst. **91**:138 (Aug.) 1950. Decker, P.: Cure opératoire d'une fistule aorta-cave, Helvet. chir. acta **17**:3 (March) 1950.

APPARENT TWO-YEAR CURE OF NEPHROGENIC HYPERTENSION

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THE VALUE of nephrectomy as a possible cure for hypertension in patients having unilateral renal disease has been the subject of markedly divergent opinions. Braash,[1] after presenting the favorable two-year follow-up data of 100 patients who had nephrectomy, concluded that his results should eliminate doubt that unilateral renal lesions can cause hypertension and that removal of a diseased kidney can effect cure. His patients had no symptoms of urological disease and were operated upon solely to cure their hypertension. Smith,[2] on the other hand, reached a less optimistic conclusion after a critical analysis of 47 reported cures as well as a thorough review of the literature pertaining to unilateral renal disease as a cause of hypertension. He stated that the advisability of nephrectomy must rest upon recognized surgical indications and not upon the hope of reducing hypertension.

The following case report presents an apparent two-year "cure" of hypertension after the removal of a nonfunctioning aplastic kidney. This kidney was neither the seat of any clinically detectible infection nor was it causing any apparent symptoms. The sole indication for the surgical removal of this organ was the hope that its excision might decrease the persistently elevated blood pressure.

REPORT OF A CASE

E. M., a 17-year-old white girl, was admitted to the Maimonides Hospital of Brooklyn in May, 1950, complaining of intermittent bilateral frontal headaches of two years' duration. Eighteen months prior to her hospitalization, during a routine physical examination, hypertension was observed for the first time. Despite marked limitation of physical activity and dietary salt restriction, the systolic blood pressure ranged from 150 to 180 mm.; the diastolic blood pressures are not known.

Past history revealed that the patient had had scarlet fever at the age of 7 years. Urinalyses never demonstrated either albuminuria or pyuria. Enuresis had persisted to the age of 16 years. There was no known genitourinary, hypertensive, or cardiovascular disease in the family.

Physical examination demonstrated systolic blood pressures of 150 to 195 mm. and diastolic blood pressures of 105 to 140 mm. The blood pressure in the legs was 145/95. The fundi oculi were normal. The heart did not appear to be enlarged. The aortic second sound was accentuated and there was a Grade 2 apical systolic murmur, which was not transmitted to the axilla. There was no evidence of cardiac decompensation. No abdominal mass was palpated. Each dorsalis pedis pulsation was normal.

From the Departments of Medicine and Surgery (Urology), Maimonides Hospital of Brooklyn, and the College of Medicine, State University of New York at New York City.

1. Braash, W. F.: End Results Following Nephrectomy in Patients with Hypertension, J. Urol. **68**:6, 1952.

2. Smith, H. W.: Hypertension and Urologic Disease, Am. J. Med. **4**:724, 1948.

Repeated urinalyses failed to show any albuminuria or pyuria. The highest specific gravity of the urine was 1.025. The hemoglobin was 70% of normal and the red blood cell count was 4,000,000 per cubic millimeter. No blood was found on chemical analysis of the stool. The venous pressure was 85 mm. of saline and the dehydrocholic acid (Decholin) circulation time was 8 seconds. The x-ray study of the heart disclosed a cardiothoracic ratio of 9.8/23. The electrocardiogram showed a high R wave in Lead aVf and an accentuated convexity of the ST segment in Lead V_6; these were ascribed to left ventricular strain. The serum urea was normal. The urea clearance values averaged 105%; the two hour excretion of phenolsulfonphthalein was 48%. Upon the intravenous administration of piperoxan hydrochloride (Benzodioxane), the blood pressure rose from 165/125 to 185/130; there was no fall below control levels. During a cold pressor test the blood pressure rose from 150/120 to 185/135. The lowest blood pressure recorded was 130/95; this was obtained while the patient was asleep under the effects of amobarbital (Amytal) sodium.

An intravenous pyelogram revealed a normal right kidney and calyces. The left kidney was not seen. During cystoscopy urine could be obtained only from the right ureter. This urine was normal and sterile. After intravenous administration, dye was seen to come from the right

Clinical and Laboratory Findings in a Hypertensive Patient Before and Two Years After Nephrectomy

	Before Nephrectomy	2 yr. After Nephrectomy
Blood pressure		
Systolic range	150-195 mm.	105-128 mm.
Diastolic range	110-135 mm.	75-90 mm.
During effect of amobarbital (Amytal) sodium	135/95 mm.	100/75 mm.
During cold pressor test	185/135 mm.	128/90 mm.
Apical systolic murmur	Present	Absent
X-ray of heart		
Cardiothoracic ratio	9.8/23	9.0/23
Left lower cardiac contour	Round	Flat
Electrocardiogram		
Lead AVF	High R wave	Normal
Lead V_6	Accentuated convexity of ST	Normal
Urea clearance	105%	125%
Phenolsulfonphthalein excretion	48%	70%

ureter at a normal rate and concentration; no dye came from the left ureter. A retrograde pyelogram demonstrated a slightly rotated left kidney with calyceal distortion and elongation. The interpretation by the roentgenologist suggested the possibility of a congenital defect.

At operation a small aplastic left kidney, weighing 10.5 gm., was removed. The cortex and medulla were poorly differentiated. The pelvis and calyces, which were of normal size, appeared disproportionally large, owing to the marked thinning of the renal parenchyma. Microscopic examination revealed no glomeruli and marked parenchymal atrophy. Sclerosis was present in both the arterioles and the arteries.

A gradual drop of blood pressure began on the fifth day after the atrophic kidney was removed. By the 10th day the systolic blood pressure was 110 to 120 mm. and the diastolic pressure was 70 to 85 mm.

For two years the patient remained without symptoms and was normally active. There were no dietary restrictions. The blood pressure remained in the normal range. In April, 1952, the patient was admitted to the Maimonides Hospital for reevaluation of her renal and vascular status. The blood pressures and renal functions were all normal. The signs which were suggestive of left ventricular strain in the electrocardiogram taken two years previously were no longer present at this time. However, the interpreter of the electrocardiogram stated that conclusions covering any differences between the two tracings had to be made with caution, because only a single preoperative tracing was available. The data obtained during the second hospitalization can be compared with similar data obtained prior to nephrectomy as presented in the Table.

COMMENT

In 1934, Goldblatt [3] demonstrated in animals that renal anoxia of one kidney could cause severe hypertension which disappeared upon removal of that ischemic kidney. In the 15 years that have elapsed since Butler [4] first removed a kidney in a successful attempt to cure hypertension, many kidneys have been removed, usually without prolonged beneficial effect upon the blood pressure. Smith [2] reported that good results were obtained in only 19% of patients subjected to nephrectomy. On the other hand, Brash [1] reported that 64% of his subjects had significantly lower blood pressure two years after nephrectomy.

All the authorities agree that if the unilateral renal lesion requires removal because of the local disease process, it should be removed in the hypertensive as well as in the normotensive patient. However, there is disagreement as to the advisability of removing an uninfected aplastic kidney, which is causing no local symptoms, solely to treat hypertension. As previously mentioned, Smith [2] advised against the surgical removal of these kidneys.

Schroeder and Fish,[5] in 1940, proposed five indications for unilateral nephrectomy in the treatment of nephrogenic hypertension. These are (1) the onset of hypertension should have occurred within two years, (2) the renal lesion should be unilateral and should be of such a nature as to decrease the function solely of one kidney, (3) the renal function as measured by total urea clearance and ability to concentrate urine should be normal, (4) retinopathy should be absent or minimal, and, finally, (5) the blood pressure should be persistently elevated prior to surgery. The patient presented in this report had all five of these indications for nephrectomy and has had an apparent two year "cure" of her previous hypertension. Mathisen [6] has recently reported a two year "cure" of hypertension in a 13-year-old girl who also fulfilled all five criteria of Schroeder and Fish. Thus it would seem that surgery should be considered as a possible cure for hypertension if severe unilateral renal disease exists.

Barker [7] reported that 1% of hypertensive subjects had pyelographic evidence of significant or advanced unilateral lesions. He advised that surgical removal be limited only to those chronic pyelonephritic kidneys which are markedly reduced in size, provided the other kidney has normal size and function. Of the 100 patients subjected to nephrectomy in order to treat hypertension, 54 had advanced unilateral renal atrophy and fibrosis as demonstrated by decrease in unilateral renal function and by decrease in renal weight below 85 gm. Our patient had no demonstrable

3. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension: The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59**:347, 1934.

4. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Invest. **16**: 889, 1937.

5. Schroeder, H. A., and Fish, G. W.: Studies on "Essential" Hypertension: The Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, Am. J. Med. Sc. **199**:601, 1940.

6. Mathisen, H. S.: Arterial Hypertension in Unilateral Renal Disease with Inhibition of Growth, Treated with Nephrectomy, Acta med. scandinav. **139**:421, 1951.

7. Barker, N. W.: Symposium on Diseases of Kidney: Hypertension and Unilateral Renal Disease, M. Clin. North America **35**:1041, 1951.

function of a mere 10 gm. atrophic kidney. It is suggested that marked reduction in size of the diseased kidney be added as a sixth criterion for nephrectomy to treat hypertension.

Perera and Haelig,[8] in a recent report on apparent "cures" of hypertension after unilateral nephrectomy, emphasize the observation that the clinical features of this type of hypertension were characteristic of so-called "malignant" hypertension. Fourteen of their 20 subjects showed definite severe retinopathy, and the hypertension was acute, severe, and rapidly progressing. In addition, they point out that in many of their subjects hypertension developed after the age of 50 years. Both our patient and that of Mathisen were young, and their conditions did not fulfill the clinical criteria of so-called "malignant" hypertension. Thus it would appear that there are at least two clinical types of hypertension which can be "cured" by unilateral nephrectomy.

Frequently, despite clinical and pathological data, it is difficult to differentiate between a small atrophic kidney of congenital hypoplastic origin and a small kidney due to shrinkage secondary to chronic atrophic pyelonephritis. Emmet and his associates[9] stated that they were unable to differentiate between these two causes of small unilateral kidneys by means of pyelographic criteria, of histologic criteria, or of the therapeutic effectiveness of nephrectomy on hypertension. They concluded that all instances of small unilateral kidneys should be considered as a single condition rather than split into different etiological groups. The pyelographic and pathological description of the kidney of our patient agrees in every detail with the findings in the atrophic kidneys reported by Emmet and his associates.[9]

SUMMARY AND CONCLUSIONS

A unilateral atrophic kidney of a 17-year-old female hypertensive patient was removed solely for the purpose of lowering a persistently elevated blood pressure. The atrophic kidney was free of infection and caused no local symptoms. Normal blood pressures were obtained consistently during a two year period after nephrectomy.

Hypertension, per se, would seem to be an adequate indication for the surgical removal of an asymptomatic atrophic hypofunctioning kidney if the other kidney is of normal size and function. This is especially true if the patient is young, if the hypertension is of short duration, and if retinopathy is absent or minimal. It would, therefore, be advisable to obtain pyelographic studies of all hypertensive patients who have normal renal function as measured by urea clearance and urinary concentration tests. By this means the unilateral asymptomatic atrophic kidney, which may be causing hypertension, could be found, with resultant increase in the surgical cure of nephrogenic hypertension.

Dr. William Dressler, Dr. Morris Slobodkin, and Dr. Abraham R. Kantrowitz interpreted the electrocardiographic tracings, the x-ray films, and the gross and histological pathology specimens, respectively.

8. Perera, G. A., and Haelig, A. W.: Clinical Characteristics of Hypertension Associated with Unilateral Renal Disease, Circulation **6**:549, 1952.

9. Emmet, J. L.; Alverez-Ierena, J. J., and McDonald, J. R.: Atrophic Pyelonephritis Versus Congenital Renal Hypoplasia, J. A. M. A. **148**:1470, 1952.

INTESTINAL MYIASIS FROM RAT-TAILED MAGGOTS IN A WOMAN

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THE OCCURRENCE of gastric myiasis in humans has occasionally been reported in medical literature; however, not without considerable discussion regarding the authenticity of the reports from various observers. What appears to be an authentic case of its occurrence in a woman was briefly presented by us at the annual meeting of the Colorado State Medical Society held in Denver on Sept. 18-21, 1951.[1]

REVIEW OF THE LITERATURE

In 1909, McCampbell and Corper [2] cited a case of intestinal myiasis attributed to three species of dipterous larvae; among these was the rat-tailed maggot, Eristalis tenax. The patient was a farm woman living in Ohio. She had intermittent spells of abdominal distress over a period of years, accompanied by colicky pains, nausea, and vomiting. Cathartics were necessary to relieve constipation. After the administration of magnesium sulfate (Epsom salts) larvae were usually passed in liquid stools.

The authors give a brief history of the life and occurrence of the so-called drone fly, the common name of the adult rat-tailed maggot, without suggesting treatment or presenting the final history of the case.

A case discussed by Hall and Muir, which occurred in 1912,[3] was that of a 5-year-old boy living at Colorado Springs, Colo.

After 10 weeks of illness the lad experienced indigestion and obstinate constipation; he became anemic and emaciated, with twitching of the eyelids and grinding of the teeth, muscular pains, and headache, and his breath was reported "like a rotten egg." The mother of the boy was advised to give a proprietary worm remedy. The following day he passed a wriggling object in his stools which was identified by Hall as a rat-tailed larva. A second maggot was reported passed the next day.

At the time this paper was presented before the State Medical Society Dr. Stiles was Chief, Laboratory Section, Colorado Department of Public Health, Denver, and Dr. Cleland was Health Officer and a practicing physician at Delta, Colo.

1. Stiles, G. W., and Cleland, W. S.: Intestinal Myiasis from Rat-Tailed Maggots in a Woman, read before Colorado Medical Society, 81st Annual Session, Denver, Sept. 18-21, 1951.

2. McCampbell, E. F., and Corper, H. J.: Myiasis Intestinalis Due to Infection with 3 Species of Dipterous Larvae, J. A. M. A. **53**:1160-1162 (Oct. 9) 1909.

3. Hall, M. C., and Muir, J. T.: A Critical Study of a Case of Myiasis Due to Eristalis, Arch. Int. Med. **11**:193-203 (Feb.) 1913.

Mackie, Hunter, and Worth [4] say

The "rat-tail maggots," of the genera *Tubifera (Eristalis)* and *Helophilus* are capable of adapting themselves to the human intestinal tract. Nasal myiasis due to larvae of this group has also been recorded. The drinking of water from foul ditches or puddles is probably responsible for all cases of human infection. In nature the maggots hang head downward in the water, the posterior extremity of the elongate "tail-like" portion piercing the surface film. They thus derive oxygen from the atmosphere, but are otherwise completely submerged. The adult flies often show a remarkable resemblance to bees.

In Herms' "Medical Entomology" [5] a definite word of caution is given against accepting all reports that rat-tailed maggots have actually been evacuated from patients with bowel discharges. However, the author discusses the case of Hall and Muir and apparently agrees that the evidence presented by them justifies their claims of rat-tailed maggot infestation in a 5-year-old boy.

Herms further describes the rat-tailed larvae as follows:

Tubifera (= Eristalis) tenax (Linn.), the drone fly is a large insect, somewhat larger than a honeybee and resembling the drone bee very closely; indeed it is commonly referred to as its mimic. The fly deposits its eggs on liquid manure or other filthy liquids in cans, slop jars, privies, septic tank effluent, etc. The larvae are known as "rat-tailed larvae"; these also occur occasionally in heaps of horse manure.

The family *Syrphidae* includes a very large group of flies, varying greatly in size, many of which are brightly colored. They are nearly all flower loving, feeding on nectar mainly. Only one genus needs to be considered here, namely *Tubifera*, the larvae of which have a long anal breathing tube, i. e., "rat-tailed," and the adults of which are commonly called drone flies.

Metcalf [6] advises that there are no insects that habitually live in the human alimentary canal; however, the eggs or small larvae of various flies, including the rat-tailed maggots, may be swallowed with impure drinking water or with infested overripe fruit or foods.

In the tropics various species of maggots may live in the flesh of the human body; however, the author points out that this is exceptional and considers it to be accidental under normal conditions in temperate zone America.

Intestinal myiasis may be caused by the larvae of the house, latrine, pomace, and several kinds of flesh flies, including rat-tailed maggots.

Metcalf describes the usual symptoms as nausea, vomiting, severe abdominal pains, and sometimes a bloody diarrhea terminating in the passage of maggots with the excrement. The recommended control measures are reasonable care about eating uncooked meats, vegetables, and fruit.

The mouths, nostrils, and other body openings of children should be protected against attacks of flies by netting or other devices.

The following correspondence from Pratt [7] has a direct bearing on this subject.

4. A Manual of Tropical Medicine, prepared by Mackie, T. T.; Hunter, G. W., III, and Worth, C. B., of the National Research Council, Division of Medical Sciences, Philadelphia, W. B. Saunders Company, 1945, p. 609.

5. Herms, W. B.: Medical Entomology, with Special Reference to the Health and Well-Being of Man and Animals, Ed. 4th, 1950, pp. 376-378, New York, The Macmillan Company.

6. Metcalf, C. L., and Flint, W. P.: Destructive and Useful Insects: Their Habits and Control, Ed. 3, revised by R. L. Metcalf, New York, McGraw-Hill Book Company, Inc., 1951, pp. 28 and 997.

7. Pratt, H. D.: Personal communication to the authors, Aug. 24, 1951.

Tubifera (Eristalis) *tenax* (Linn.), the drone fly, is a rather large fly (Fig. 211) resembling the drone bee. The adults may be seen flying over open cesspools, water heavily charged with rotting animal matter, and liquid manure and about open privies, the effluent from septic tanks, etc., near or on which they deposit their eggs. The larvae are very distinctive and are known as "rat-tailed maggots." Though their larval habitat should migrate against human infection, a rather large number of cases of intestinal myiasis of man caused by the larvae of this or related species is on record. Hall and Muir (1913) carefully investigated all known cases and listed 13, 12 intestinal and 1 nasal. In 1918 Hall [Hall [8]] recorded another case in a boy 18 years of age. This patient passed a rat-tailed maggot in his stool. The symptoms were intense irritation of the rectum. At this time a total of *20* cases were listed—18 in man (17 intestinal, 1 nasal) and *2* (vaginal) in cows. Since then Pumpelly has reported a case in a man *30* years of age, residing in Virginia. The patient, suffering from constipation, had passed worms in his stools. Treatment with carbon tetrachloride resulted in the evacuation of six larvae, all *Tubifera tenax*. Another case has been reported from Argentina, a 15 month-old child evacuating larvae after treatment, and one from the Federated Malay States. Bruce has also reported a case of vaginal myiasis in a cow in British Columbia. The vagina was diseased and the author thinks the fly deposited her eggs directly on the exudate. In all, 12 maggots were recovered. Swartzwelder (1942) reports removing 7 maggots after treatment of a six-year old child in Louisiana.

Infection with *Tubifera* larvae would seem possible only from drinking fouled water containing young larvae or eggs, from soiling the hands with wastes on which young larvae or eggs were present, from eating unwashed water cress obtained from filthy water, or in some cases from eating rotting fruit. Though *T. tenax* is the most commonly reported species whose larva causes myiasis, other species, *T. arbustorum* and *T. dimidiatus*, have also been incriminated. It may be pointed out here that species identification of Tubifera larvae is probably impossible at present. All specific references, except where the adult has been reared, should be regarded as doubtful. *T. tenax* is, however our most common species, world-wide in distribution, and numerous cases of infestation have been reported.

REPORT OF A CASE

Mrs. E., a 45-year-old housewife, residing near Delta, Colo., first consulted a chiropractor in October, 1950. A very complete and thorough physical examination, including the history, symptoms, and other pertinent data, was obtained from the patient on Aug. *22*, 1951, by one of us (W. S. C.).

The patient had had the usual childhood diseases, without serious sequelae. She had been in poor financial circumstances since the death of her husband, two years before; consequently her living and eating habits were below standard. Between attacks of intestinal parasitism her health was fairly normal, except for tiredness and general weakness.

The illness began, late in 1948, with severe abdominal cramps, accompanied by swelling or bloating of the face and abdomen and pains in the arms and legs.

Many parasites were reported to be expelled with the patient's bowel movements following the use of enemas, various cathartics, or worm remedies. This woman's daughter declares that she could usually predict the onset of an attack because of her mother's "very foul breath."

For more than three years this patient had complained of poor health, capricious appetite, general weakness and fatigue, and alternating constipation and diarrhea following the use of salines or purgatives.

During the attacks headache was not uncommon and nausea was frequent, with intermittent muscular spasms. These symptoms were generally accompanied by the passage of many maggots.

The chiropractor and his assistant when interviewed (by W. S. C.) on Sept. 11, 1951, stated that they saw the rat-tailed maggots passed in their office many times; that when they removed the rectal speculum after the colonic flushings there were rat-tailed maggots clinging to the instrument, and that they were also observed in large numbers in the vessels or toilet in the office.

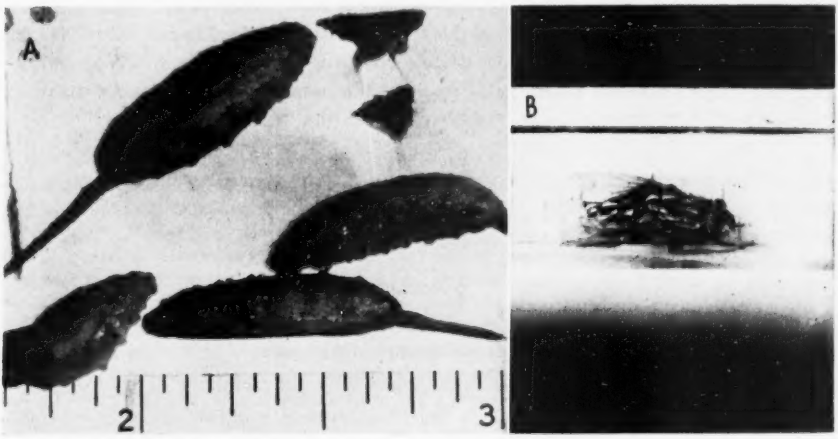
8. Hall, M. C.: A Note Regarding Myiasis, Especially that Due to Syrphid Larvae, Arch. Int. Med. **21**:309-312 (March) 1918.

Dr. Cleland states, "Dr. Kemp brought the first samples over to me and said this lady passed them by the hundreds right in his office when taking the colonic flushings."

Dr. Cleland said that the maggots usually died soon after he received them; however, a few survived and developed into adult flies. Photographs were made by him of both the flies and the maggots, as shown in the Figure. Unfortunately the adult flies died and quickly disintegrated soon after maturing; consequently they were not submitted for species identification, as suggested in Pratt's letter.[7]

A specimen of feces containing maggots from the patient was submitted by Dr. Kemp to the city health officer (W. S. C.) for his consideration. Since the parasites were unusual in appearance, they were sent to Dr. Geno Saccomonno, pathologist for St. Mary's Hospital, Grand Junction, Colo., who forwarded them for identification to Dr. David L. Belding, formerly of the Massachusetts General Hospital, Boston. They were classified by him as "rat-tailed" maggots, Eristalis tenax, sometimes known as Tubifera tenax, of the family Syrphidae.

On Oct. 25, 1950, Dr. Cleland sent Dr. Stiles a specimen of feces from the patient, containing approximately 50 rat-tailed larvae. Unfortunately, they were all dead on arrival; hence it was impossible to obtain adult flies from them.



A, rat-tailed maggots collected from Mrs. E.; *B*, adult fly pupated from rat-tailed maggots passed by Mrs. E.

Samples of these parasites were delivered to various entomologists and scientists for identification. Among these were Herbert Gates, Chief, Division of Plant Industry, Colorado State Department of Agriculture; Dr. Lawrence Avery, George Washington University Hospital, Washington, D. C.; Dr. H. D. Pratt, United States Public Health Service, Chamblee, Ga., and Dr. Benjamin Schwartz, Parasitologist, United States Bureau of Animal Industry, Washington, D. C. All these authorities considered the specimens to be "rat-tailed" maggots.

Epidemiology.—The initial parasitic infestation in the patient probably dated from the autumn of 1948, when she camped in the mountains near a sheep camp and drank ditch water draining the manure from the corral.

It is assumed that the manure was heavily infested with eggs deposited by the adult drone fly during the summer and that they entered the woman through the medium of contaminated water. While there appears to be a debate as to the fate of rat-tailed maggots or the adult fly eggs in the human intestinal tract, the recurring attacks in this case would suggest repeated exposure to sources of infestation during the prolonged period of illness. We do not believe that a single ingestion of contaminated water or infested food would result in so long a time of sickness, characterized by intermittent attacks and remissions, indicating probable multiple exposures.

The home conditions of this person were conducive to exposure to parasitic infestation from the consumption of over-ripe fruits, nearness of the outdoor toilet to the kitchen, and lack of modern sanitary facilities, and careless personal habits.

TREATMENT

The treatment recommended by Avery [9] is considered by him as largely experimental for infestation with rat-tailed maggots. He states there are no recent records of treatment in the "Index Catalog to Parasitological Literature," and his experience with Eristalis under field conditions indicated that members of this genus are very difficult to kill with the usual insecticides. In the digestive tract they will probably prove equally hardy.

Avery suggests giving five capsules of 0.2 gm. of hexylresorcinol (Crystoids or Caprokol) on an empty stomach followed in about two hours with a saline purgative, such as sodium phosphate (Fleet's Phospho-Soda) or sodium sulfate (Glauber's salts). Stools may be screened to ascertain the results. After four or five days, the treatment may be repeated or 3 cc. of tetrachlorethylene may be used for the second treatment. For the latter treatment, the patient should be on a low-fat alcohol-free diet for a few days. The drug should be followed by purgation in a couple of hours, as the drug often just temporarily anesthetizes the maggots and the purgative gets them out of the gastrointestinal tract.

The latest information from Dr. Cleland, as of Feb. 7, 1953, indicates that the patient has not passed any parasites since he recently gave her three treatments similar to those recommended by Avery with hexylresorcinol and that she is now in better health than she has been for years.

SUMMARY

A case is presented of probable intestinal myiasis in a 45-year-old housewife, which extended over a period of approximately three years.

The initial infestation was doubtless caused by the drinking of contaminated ditch water draining a sheep camp in the mountains of Colorado.

Evidence presented showed that the patient passed large numbers of rat-tailed maggots at frequent intervals during her period of illness and that with adequate treatment her symptoms subsided and she returned to normal health.

9. Avery, L.: Persnal communication to the authors, March 19, 1951.

Books

Liver Injury: Transactions of the Eleventh Conference, 1952. Edited by F. W. Hoffbauer, M.D. and sponsored by the Josiah Macy, Jr. Foundation. Price, $4.00. Josiah Macy, Jr. Foundation, 656 Park Ave., New York 21, 1953.

These Transactions of the Eleventh Conference supported by the Josiah Macy, Jr. Foundation are as good as those Transactions which have preceded it. The provocative article by George S. Mirick on infective hepatitis is well worth careful study, and the chapter on morphology by M. Hans Elias is certainly a classic which will be referred to many times. Other brief chapters likewise are interesting, particularly for those individuals who are devoting a great deal of their time to the study of the liver. As in the past, this is not a book for the uninitiated physician but is especially of value to those interested in gastroenterology and especially those concerned with disease of the liver.

The Auricular Arrhythmias. By Myron Prinzmetal, M.D. and others. Price, $16.50. Pp. 387, with 514 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952

This monograph is a compilation of the experimental observations on various auricular arrhythmias. The observations include high-speed motion pictures, which are correlated with electrocardiographic as well as oscillographic records. The data are presented clearly, and the numerous figures are printed well. In many instances diagrams are superimposed on the photographs, which adds to the clarity of the presentation. Without such labeling many of the photographs would be meaningless to the reader.

The authors make a convincing presentation for their concept of the unitary nature of the auricular arrhythmias. With the application of aconitine and continued electrical stimulation, the relationship of auricular premature contractions, auricular paroxysmal tachycardia, auricular flutter, and auricular fibrillation seems to be one of degree or rate. During the arryhmias occurring under the circumstances of these studies, a circus movement is apparently not present. This does not exclude the existence of circus movement flutter under other circumstances.

There is some lack of organization, with needless and sometimes monotonous repetition of the controversy with previous investigators. This extends beyond that necessary for emphasis.

There are numerous small points which are controversial and others which are overemphasized even had they been new observations, but these are generally unimportant in the presentation and in the interpretation of the mechanisms involved. One might question a statement in the preface that, unlike the electrocardiogram, which is subject to errors in interpretation, the approach by means of motion pictures affords an unequivocal record of the events as they occur in the auricles. The interpretation of the sense of sight is subject to error.

The chapters on the clinical aspects of the auricular arrhythmias and the pharmacology of the commonly used cardiac drugs are good reviews of these subjects and add to the general value of the monograph. The appendix adequately describes the methods and equipment. The bibliography is quite extensive. This monograph should be of interest to all who are interested in heart disease.

Physiological Bases of Gynecology and Obstetrics. S. R. M. Reynolds, Ph.D, D.Sc., Price, $5.50. Pp. 156. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

The book is a collection of fifteen lectures given by the author at the Facultad de Medicina de Montevideo. The style is very readable and the contents are interesting. Much of the material represents conclusions drawn from work with experimental animals and might not be valid for human beings. While the conclusions present little of practical value to the clinician, they should stimulate interest among those doing research. The clinician will gain from this book an appreciation of the complicated mechanisms governing uterine physiology.

Nerve Impulse: Transactions of the Third Conference, March 3-4, 1952, New York. Edited by H. Houston Merritt, MD. Price, $3.50. Pp. 176, with 16 illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1952.

This book should interest not only neurophysiologists but also pharmacologists and physiologists generally as well as all who are concerned with bioelectric phenomena. The Transactions include a discussion of the electrical and biochemical similarities and differences between synoptic transmission and axonal conduction and the structure of synoptic functions. It is possible to learn from this "Transactions of the Third Conference on Nerve Impulse" not only the state of our knowledge today concerning these problems but also the reactions to existing concepts of many persons interested in these problems. This book is recommended to those who wish to learn more about these selected aspects of the nerve impulse transmission.

Connective Tissues: Transactions of the Third Conference. Edited by Charles Ragan, with many contributors. Price, $3.50. Pp. 166, with illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1952.

This "Transactions of the Third Conference on Connective Tissue" is presented in essentially the same manner as all the Macy Conferences. Although the reader cannot profit as much from the Transactions as those who were present at the conference profited from the discussion themselves, this book should interest all who work with corticotropin and cortisone in the laboratory or who treat patients with these drugs. Furthermore, the Transactions contains interesting material on the fine structure of connective tissue, including excellent electromicrograms illustrating the architecture of connective tissue. Connective tissue staining, the nature of reticulin, and hypersensitivity and the hyperadrenal state are also discussed. The questions asked and the replies, as usual, should interest the reader from many points of view. This book is highly recommended to all persons in medicine, including medical students.

Morbus Alzheimer and Morbus Pick: A Genetic, Clinical and Patho-Anatomical Study. By Torsten Sjögren, Hakon Sjögren and Åke G. H. Lindgren, translated by Donald Burton. Price, not given. Pp. 152, with 12 illustrations. Ejnar Munksgaard Forlag, Nørregade 6, København, K., 1952.

This monograph is divided in 3 parts, each of which is reviewed in a separate paragraph.

T. Sjögren has arrived at the surprising conclusion that about 10% of all presenile and senile psychoses fall under the diagnosis of Pick's or Alzheimer's disease. The average age at which these diseases begin and at death is about the same in patients with either disease, and the duration of the diseases is also the same (based on material of 80 cases). The genetic statistical analysis shows a predominant likelihood of multifactorial inheritance for Alzheimer's disease. For Pick's disease the hypothesis of a major gene with modifying genes appears more acceptable. In both diseases there is a predilection for women, a fact not explainable by a totally or partially sex-linked inheritance.

H. Sjögren's clinical analysis of 80 cases shows that aspontaneity in Stage I is predominant in both diseases. Moria and pronounced ethical defects characterize the majority of patients with Pick's disease in Stage I. Alzheimer's disease even at an early stage shows typical disorientation in space; much less disorientation of time. Also noticeable in this condition is a fixed forward stare. There appears to be a disturbed association between visual and kinetic functions. In Stage II, patients with Alzheimer's disease show progressive dementia and aphasia (100% of the amnestic, 83% of the sensory type), agraphia (83%), apraxia (72%), and dysarthria (67%). Aspontaneity is predominant and hyperactivity only temporary. Central facial paresis was found in 10 out of 18 patients at autopsy; 4 had convulsions. The patients with Pick's disease also showed progressive dementia and aphasia. The significant difference between patients with morbus Alzheimer's disease and those with Pick's disease is a peculiar disturbance in gait, with pronounced increase of muscle tonus, found only in patients with Alzheimer's disease. These patients show in the incipient phase of walking a synchronous start of the motor impulses, resulting in a momentary locking of the motor phases. There is a disturbance in rhythm and coordination of movements. The gait is slow, unsteady, and clumsy, but without propulsion. Closing of the eyes has no effect. The author ascribes this disturbance to a lesion in the prefrontal region, different from that causing a Parkinsonian gait. The initiative to walk

is greatly diminished. In the terminal Stage III a true basal ganglia syndrome with *marche a petits pas* occasionally develops. Other signs of frontal lobe damage in Alzheimer's disease are the lack of initiative, affecting thought, speech, and motility, and the frequent enuresis. Basal ganglia lesions occur occasionally in Pick's disease, but clinical signs are usually absent. In the end-stages both diseases show brain atrophy, and both lead to a terminal picture of cachexia, strangely in contrast to the morbid hunger and enormous intake of food which occur in them.

A. G. H. Lindgren discusses Pick's disease and Alzheimer's disease from the viewpoint of pathology. Distinguishing characteristics are cerebral atrophy, which is more diffuse in Alzheimer's disease, more circumscribed in Pick's disease; changes in the basal ganglia, which are regular in Alzheimer's disease, exceptional in Pick's disease; fibrillar changes and plaques, which occur regularly and only in Alzheimer's disease; ballooned cells, which occur only and regularly in Pick's disease.

Dystrophia Musculorum Progressiva: Clinical and Diagnostic Criteria, Inheritance. By Herman Levison. Price not given. Pp. 176, with illustrations. Ejnar Munksgaard, Nørregarde 6, København, K., 1951.

This is a most thorough study of Dystrophia Musculorum Progressiva from a clinical point of view. The author, after reviewing the copious literature, discusses the clinical criteria (findings, features of the disease, course, and prognosis), the diagnosis (with particular reference to muscle biopsy, electromyography, acetylcholine-test, creatine-urea-metabolism), the differential diagnosis, in all its many aspects, of muscular as well as neurological disorders, the heredity (including 110 cases investigated by the author himself), and the etiology of the disease.

The conclusion from this impressive work is that dystrophia musculorum progressiva is hereditary, with overwhelming dominance for the facioscapulohumeral type. The scapulohumeral type seems to be predominantly sporadic, and its inheritance cannot be definitely established. The lower-extremity types show an incidence of less than the expected 25% of recessive inheritance, which may be explained by decreased manifestation or intermingling of acquired cases. The diagnostic criteria mentioned above show no difference between the different types of dystrophia musculorum progressiva; they only help to establish the diagnosis of the muscular disease as opposed to that of a nervous disorder. The different clinical types may belong to the same nosological unit, although there may be different genes for the three main types. One may assume that in this, as in other hereditary diseases, the more benign type is inherited dominantly and the more malignant types recessively.

Case histories of 98 families are given as an appendix to this study.

Basedow's Disease. By Hubert Sattler, English translation by G. W. Marchand and J. F. Marchand. Price, $10.00. Pp. 605. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1952.

This book is an English translation of the original German work, first published in 1880 and revised in 1908. It contains a complete review of every aspect of Graves's disease, or Basedow's disease, as the condition is known in the older German literature. Particularly interesting is the section dealing with the geographic distribution, course, duration, and prognosis of untreated Graves's disease. In these days of isotopic medicine, it is easy to forget what astute clinical judgment and observation physicians of previous decades could bring to bear on the ailments of their patients. Dr. Sattler has demonstrated this to a remarkable degree. This book should become a valuable reference source for anyone interested in the historical background, as well as in a detailed clinical description, of Graves's disease.

The Treatment of Injuries to the Nervous System. By Donald Munro, M.D., F.A.C.S. Price, $7.50. Pp. 284, with 47 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St, Shaftesbury Ave, London, W.C. 2, 1952.

"Treatment of Injuries to the Nervous System" by Dr. Donald Munro, deals with injuries to the central nervous system found in the intracranial and spinal cavities and with injuries

to the peripheral and autonomic nervous systems. This book is not only of interest to neurological surgeons, who take care of injuries to the nervous system; it should also be utilized by practitioners and house officers who take care of injured patients.

There are very excellent sections which deal with problems ordinarily neglected: transportation; treatment of associated injuries; bowel and bladder management; fluid, food, and drug administration; and such important considerations as the use of restraints and positions. Not all neurological surgeons will agree with the precise management of each injury to the nervous system, but little argument can be found with the problems of nursing care as outlined in this book. Fortunately, the author had no compunctions against mentioning names of drugs, dosage of drugs, size of catheters and types of materials to be used. There are excellent discussions and illustrations of rehabilitative devices. The greatest portion of the book is devoted to the treatment of spinal cord injuries. In the treatment of patients suffering from these afflictions, probably more complications are encountered than in any other type of problem. If the regimens of this book were followed, many fewer complications would occur, and many helpful suggestions are given for the inevitable complications which will occur in these unfortunate patients.

The neurosurgical clinic of Boston City Hospital has long enjoyed a fine reputation for its handling of traumatic neurosurgical lesions. This book not only outlines specific neurosurgical procedures which must be employed, but, even more important, it emphasizes the details of essential nursing attention too often neglected.

X-Ray Diagnosis of Chest Diseases. By Coleman B. Rabin, M.D., assistant clinical professor of medicine, College of Physicians and Surgeons, Columbia University; associate physician for chest diseases and associate radiologist, Mt. Sinai Hospital; consulting physician for chest diseases, Beth El Hospital; senior consultant for chest diseases, Veterans Administration. Price, $12.00. Pp. 508, with 288 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1952.

The author of this book on the use of roentgen rays in the diagnosis of disease of the thorax presents his material in four parts. Part I, entitled "General Considerations," deals with the principles underlying the various technics used in roentgenologic examination of the lungs and with the anatomy of the thorax from the roentgenologic standpoint. An excellent discussion of the value and method of performing the roentgenoscopic examination is included.

The subject of Part II is "General Roentgen Pathology." This excellent section deals with such topics as congestion, atelectasis, emphysema, infiltration, consolidation, and cavitation in much the same manner as a teacher of pathology who expounds such basic general subjects as inflammation, degenerative changes, and formation of tumors.

Part III, "Regional Roentgen Pathology," deals with the roentgenologic manifestations of specific diseases. In this section, for example, are discussions of pneumonia, tuberculosis, sarcoidosis, and pulmonary neoplasm. Disease processes involving the structures of the mediastinum, the pleura, and the diaphragm are included. The subject of diseases of the heart and great vessels has been omitted by design, as the author has stated in his preface.

Part IV is concerned with the differential diagnosis of certain roentgenologic patterns, such as the solitary round shadow, the sharply defined linear shadow, and those multiple miliary shadows which may be produced by such a variety of lesions.

The book is enhanced by 288 well-chosen illustrations and a bibliography of 474 references. It was written and first published as a chapter in Golden's looseleaf "Diagnostic Roentgenology." Because the publishers found it necessary to use the original plates, an undesirable system of numbering the pages causes the subject matter to begin on page 63 and end on page 194P, although some 495 pages intervene. This numbering of pages and the poor reproduction of some of the halftone engravings make the reader wish that the publisher had been able to reset the type and give the author's material the setting it deserves.

The book can be recommended most highly. It is an up-to-date and authoritative exposition of a most important phase of diagnostic roentgenology. It will prove to be a valuable addition to the library of a medical student, a general practitioner, or a physician or surgeon interested in the diagnosis of thoracic disease.

Bacterial and Mycotic Infections of Man. Edited by René J. Dubos. Second edition. Price, $7.50. Pp. 886, with 98 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C. 2; 2083 Guy St., Montreal, 1952.

Viral and Rickettsial Infections of Man. Edited by Thomas M. Rivers, M.D. Second edition. Price, $7.50. Pp. 719, with illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C. 2; 2083 Guy St., Montreal, 1952.

The first editions of these useful books were well conceived and well executed. Since the editors of the second editions are the same and the group of eminent contributors very little changed, there are no radical departures in organization or extensive changes in the material presented beyond those required to bring factual knowledge up to date.

These books differ from the usual texts of bacteriology and virology in laying emphasis on host-parasite relationships rather than on the characteristics of the specific disease agents alone. For instance, in the volume on bacterial and mycotic infections about one fourth of the book is devoted to morphology and physiology of bacteria, properties of the bacteria which enable them to cause disease, response of the host to the parasite, immunochemistry, the allergic state in the host, etc. Then follows a discussion of the various types of micro-organisms with their particular effects on the human body and a brief discussion of treatment of each. The section on chemotherapy by Walsh McDermott, toward the end of the book, is splendid. Among the 37 contributors to this book are included Thomas Francis, Jr., Colin MacLeod, Jr., Howard Mueller, Homer Swift, and many others of equal caliber.

The book on viruses is organized in the same way, with more than half the pages devoted to general problems of virology, such as chemical and physical procedures, serologic reactions, chick embryo technics, tissue cultures and the like. Specific diseases are then discussed, with special emphasis on the pathologic changes induced in the host. The reviewer knows of no other volumes in which so many experts in various phases of the infectious disease field have pooled their knowledge in a two-volume text. These are not clinical texts in the sense that they devote themselves chiefly to diagnosis and treatment, but all studious clinicians will find in them much of direct value in the management of infectious disease states.

Essentials of Medical Diagnosis: A Manual for Students and Practitioners. By Rt. Hon. Lord Thomas J. Horder, G.C.V.O., M.D., F.R.C.P., extra physician to H. M. the Queen; consulting physician to St Bartholomew's Hospital, and A. E. Gow, M.D., F.R.C.P., honorary physician to Household H. R. H. the Duchess of Kent; consulting physician, St. Bartholomew's Hospital. Second edition. Revised with the assistance of Ronald Bodley Scott, M.A., D.M., physician to H. M. Household; assistant physician and senior demonstrator of practical medicine, St. Bartholomew's Hospital. Price, $6.00. Pp. 462, with 23 plates, 22 figures in the text, and 5 charts. Baltimore: Williams and Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

This book is divided into various sections dealing with the physiological systems of the body. It is aimed at teaching the art of diagnosis by the use of the human faculties as opposed to the use of purely mechanical means. It does this admirably by the logical organization of its sections. Each section begins with a brief review of the anatomy and the physiology of the organs involved, thus emphasizing to the medical student and recalling to the practitioner the application of these facts in the approach to the patient and his disease. The section proceeds to the technic of methodical examinination of the patient— the means of eliciting physical signs and their significance in diagnosis.

A brief introductory section is devoted to the taking of the medical history; the authors state what is already known consciously or unconsciously by the physician—that certain details of the history alert one for possible confirmatory signs to be found during the examination and that it is inadvisable to examine a patient without at least some tentative notions of what may be found. Important symptoms are mentioned in addition to physical signs, to give the

reader a comprehensive idea of the more common diseases. An analysis of important symptoms (headaches, unconsciousness, cough, abdominal pain, jaundice) is made in the discussion of the systems in which these are pertinent. The various sections conclude with brief mention of the auxiliary aids to diagnosis—ophthalmoscopy, lumbar puncture, thoracentesis, paracentesis, electromyography, electrocardiography, endoscopy, and clinical laboratory studies. There are chapters which detail the characteristics of urine, feces, vomitus, and sputum in disease states.

The final section, "Pyrexia," treats of the types of fevers, their characteristics, and the means of identifying their causes.

An appendix lists tables of normal values. There is a good index.

Anatomy of the Nervous System. By Stephen Walter Ranson, M.D., Ph.D.; revised by Sam Lillard Clark, M.D., Ph.D. Ninth edition. Price, $8.50. Pp. 554, with 434 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1953.

The number of editions which this book has gone through in the last thirty years tells the story of its usefulness and popularity. This edition, the ninth, is revised by Dr. Clark in place of the late Professor Ranson. The book deals systematically with the anatomy of the central nervous system and does not lend itself to a detailed review. However, as a convenient reference work it seems to us highly adequate. There are many excellent illustrations; the paper and print are good. There is a bibliography and an index.

Gastric Cancer. By Alfred H. Iason, M.D. Price, $7.50. Pp. 316. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1953.

As the author states in the preface of this monograph, it is not possible in the brief span of 300 pages to cover completely a field in which so much work has been done over the years; the goal, therefore, is a succinct summary. The book represents a tremendous amount of effort and the experience of a lifetime together with a summary of numerous opinions of other workers. There is little critical analysis. The author describes many subjects with which he is not intimately acquainted. This is especially evident in the sections on pathology, gastroscopy, and exfoliative cytology. There are 20 plates in the chapter on pathology; 10 of these are pictures of squamous carcinoma, but there is no reference whatsoever in the chapter to this rare entity. The proofreading is faulty, for at least one of the x-ray films is printed upside down and some of the references are nonexistent. The chapters on surgery, anesthesia, preoperative and postoperative care, and complications are detailed. The 187 references are well selected, but they would have been more usable if arranged in alphabetical order. The paper, printing, format, and illustrations are all excellent. The book should be helpful to the general surgeon.

Modern Trends in Gastroenterology. Edited by F. Avery Jones, M.D., F.R.C.P., with many contributors. Price, $20.00. Pp. 831, with 275 illustrations. Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16, 1952.

This volume is highly recommended to all physicians and surgeons interested in the field of gastroenterology. It contains reports of a great deal of recent British and Australian work in this field, much of which might not otherwise come to the attention of American members of the medical profession. It is concerned not only with clinical advances but also with progress in the fundamental sciences underlying the practice of gastroenterology.

The book represents the work of many authors, each of whom has written a chapter or section of a chapter and each of whom was chosen because he has made recent contributions concerning his particuar subject. In general, the choice of contributors has been fortunate, and for the most part the expositions are informative, lucidly presented, and often stimulating. The names and previous publications of many of the authors will be familiar to gastroenterologists in this country.

Although it deals with most of the common disease states and clinical problems encountered in the field of gastroenterology, this volume cannot be considered a textbook on the subject, since there is no attempt to deal with all of them. Recent developments in each field are

emphasized, and most of the authors have made a commendable effort to place newer findings in relation to older work and to work done in other parts of the world. However, some sections may be criticized because the author has failed to consider pertinent and significant the work done in the United States and other countries. Such omissions have been justified by the editor, F. Avery Jones, in his introduction to the volume, on the basis of the fact that American work has been previously well covered in publications which have been more readily available than the corresponding British works.

The emphasis placed on recent development in various fields of gastroenterology makes stimulating reading in many sections of this book. Interest for American readers is further enhanced by the fresh point of view presented by many of these colleagues from distant countries. Some of the material presented is still to be confirmed or evaluated in the light of further work and experience. This very fact should encourage further research in gastroenterology, which is one of the avowed purposes of the book.

Poliomyelitis. By W. Richie Russell, C.B.E., M.D. (Edinburgh), M.A. (Oxon.), F.R.C.P. (Edinburgh), F.R.C.P. (London). Price, $3.00. Pp. 81. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2,

In poliomyelitis one is accustomed to read about pathology, physiology, and clinical problems in scattered sources. Hence, it is a delight to find this compact little volume correlating the pathophysiological processes with the clinical findings and treament dramatically illustrated by case material.

Diagnostic features, technic of physical examination, and factors influencing the course of the disease are clearly discussed. Of interest is the analysis of spinal pains and the tables reflecting the relation of physical activity to paralysis. Little is said about cerebral anoxia and its ability to mimic the symptoms of the disease. Some would be disturbed by the suggestion of home care in the face of impending paralysis and likewise by the recommendation to use barbituates. The suggestion of a mobile treatment is of interest.

A plea is made for appraisal of rehabilitation methods by adopting uniform testing procedures. The very recent advances in this field are heralded. Bits of wisdom obtained only by long experience are sprinkled throughout the volume. It should be a welcome addition to the libraries of students and clinicians.

Headaches: Their Nature and Treatment. By Stewart Wolf, M.D., and Harold G. Wolff, M.D. Price, $2.50. Pp. 177. Little, Brown & Company, 34 Beacon St., Boston 6, 1953.

This book concerning the nature and management of head pain is directed toward the layman. It is well written and avoids the use of technical terminology. The extensive experience and long-standing interest of the authors with the problem of headache are manifest in the well-organized presentation of this material. Proper emphasis is placed on the commoner types of headaches and on the emotional setting with which these headaches appear to be related.

The illustrations are clear and are pertinent to the material presented. The book is recommended for interesting reading not only for laymen but also for physicians.

Bedside Diagnosis. By Charles Mackay Seward, M.D., F.R.C.P., with Foreword by Henry Cohen, M.D. Second edition. Pp. 380. Price, $3.50. Williams & Wilkens Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

As stated in the forward, this book is based on the belief that the "causes of disease are often indicated by the grouping and mode of development of symptoms and signs."

There are 22 chapters, and each is devoted to a common symptom or sign of disease (cough, pyrexia etc.). The physiology of the symptom is first discussed. Then a diagnostic approach is presented which, if followed in its logical sequence, will lead one to study each of the diseases in which the symptom or sign is a prominent feature.

Although the book is of the handbook type, it is much more than a mere catalogue of diseases under symptom headings.

Treatment of Mental Disorder. By Leo Alexander, M.D. Price, $10.00. Pp. 507, with 143 figures and 22 tables. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1953.

This book presents an intelligent and unbiased case for the proper use of the physical methods in the therapy of mental disorders. Concomitantly, the various forms of psychotherapy are discussed, and the roles that they play in therapy are emphasized. There is described a varied approach to the problem of therapy, stressing both the physical and the psychodynamic aspects, with the proper blending of the two. Emphasis is placed upon the importance of determining the type of therapy needed at various stages in the patient's illness.

Full attention is given to the indications, methods, neurophysiological aspects, and complications of the physical methods of treatment. Among the methods discussed are electroconvulsive and nonconvulsive therapy, electric coma, insulin coma and insulin subshock, and the various forms of psychosurgery. For this reason, the book is particularly recommended to beginners in psychiatry.

Alexander's review of the literature and bibliography are definitive. There is a compilation of statistics from various published works which are informative and thought-provoking.

The Pharynx: Basic Aspects and Clinical Problems. By Abraham R. Hollender, M.D., F.A.C.S. Price, $15.00. Pp. 560, with 237 illustrations. Year Book Publishers, Inc., 200 East Illinois St., Chicago 11, 1953.

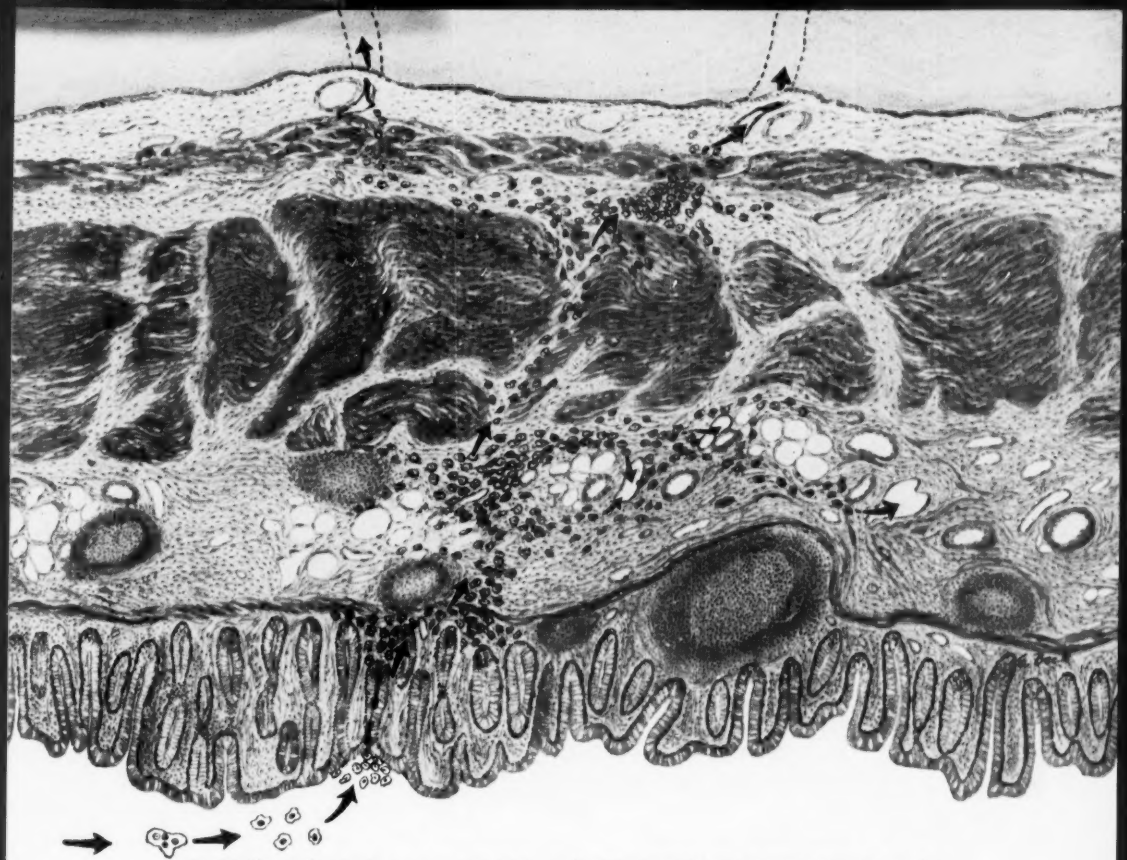
This book of over 500 pages dealing with the pharnyx is a good instance of the geographical type of textbook so popular nowadays. One finds, for example, a chapter on the pharnyx and blood diseases, in which are discussed the oral and pharangeal evidences of hemophilia, leukemia, infectious mononucleosis, agranulocytosis, etc. This sort of material rubs shoulders with the technique of tonsillectomy, infections of the neck, and roentgen examinations of the pharnyx. The reviewer will not attempt to criticize the logic of this sort of a compilation. There is certainly a great deal of useful material, and the book is profusely and well illustrated.

Symptoms and Signs in Clinical Medicine: An Introduction to Medical Diagnosis. By E. Noble Chamberlain, M.D., M.Sc., F.R.C.P. Fifth edition. Price, $8.00. Pp. 480, with 354 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

This little book includes a lot of useful material about the general examination of patients. It is not exactly a textbook of physical diagnosis but reminds one more of such books as that by Seifert and Mueller. The number of editions through which it has passed since 1936 testifies to the popularity of the book, at least in England. The illustrations are excellent and there is an index. Nonetheless, this does not seem to add a great deal to books which are readily available in this country.

Textbook of Virology. By A. J. Rhodes, M.D., F.R.C.P. and C. E. van Rooyen, M.D., D.Sc., M.R.C.P. Second edition. Price, $8.00. Pp. 561, with 76 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

The way in which virus disease has crowded out ordinary bacterial infections is well illustrated by the number of monographs on virology, which now appear with increasing frequency. This volume follows the usual procedure of giving first a general discussion about viruses, their biology, their epidemiology, and the technical methods of dealing with them. This is followed by discussions of individual diseases. Although the book runs to 550 pages, the clinical discussions are quite brief, which shows how large the subject has become. This seems to the reviewer to be an excellent book, which is quite adequate for orientation in the domain of viruses.



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*Weingarten, M.: Proctology Symposium: Amebiasis: Medical Aspects, Mod. Med. *20*:121 (May 15) 1952.

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1. Humphreys, P., *et al.*: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: N. Y. State J. Med. 52:2012 (Aug. 15) 1952.
3. Dailheu-Geoffroy, P.: L'Ouest-Méd., vol. 3 (July) 1950.

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1. Bargen: Chronic Ulcerative Colitis. Charles C Thomas, Publisher. 1951. Springfield, Illinois.

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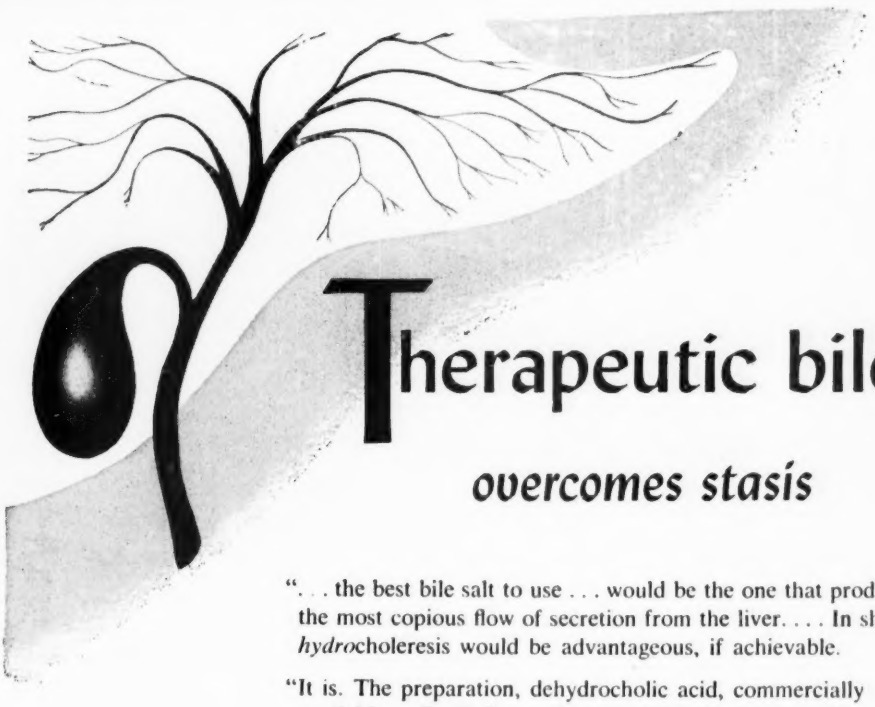

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*Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 361.

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1. Flour and Bread Enrichment, 1949-50: Prepared by The Committee on Cereals, Food and Nutrition Board, National Research Council, Washington, D.C., 1950.
2. Geddes, W.F.: Cereal Chemists Guard Nutrition, Agricultural and Food Chemistry *1*:38 (Apr.) 1953.
3. Bakery Products; Definitions and Standards of Identity, Federal Register *17*:4453 (May 15) 1952.
4. Sherman, H.C.: Chemistry of Food and Nutrition, ed. 8, New York, the Macmillan Company, 1952, p. 599.
5. Goddard, V.R., and Marshall, M.W.: The Calcium Content of Commercial White Bread, United States Department of Agriculture, Technical Bull. No. 1055, 1952.

   Crespo, S., and Bradley, W.B.: Calcium and Milk Content of Commercial White Bread. Report by the Laboratories of the American Institute of Baking, Feb. 28, 1950.

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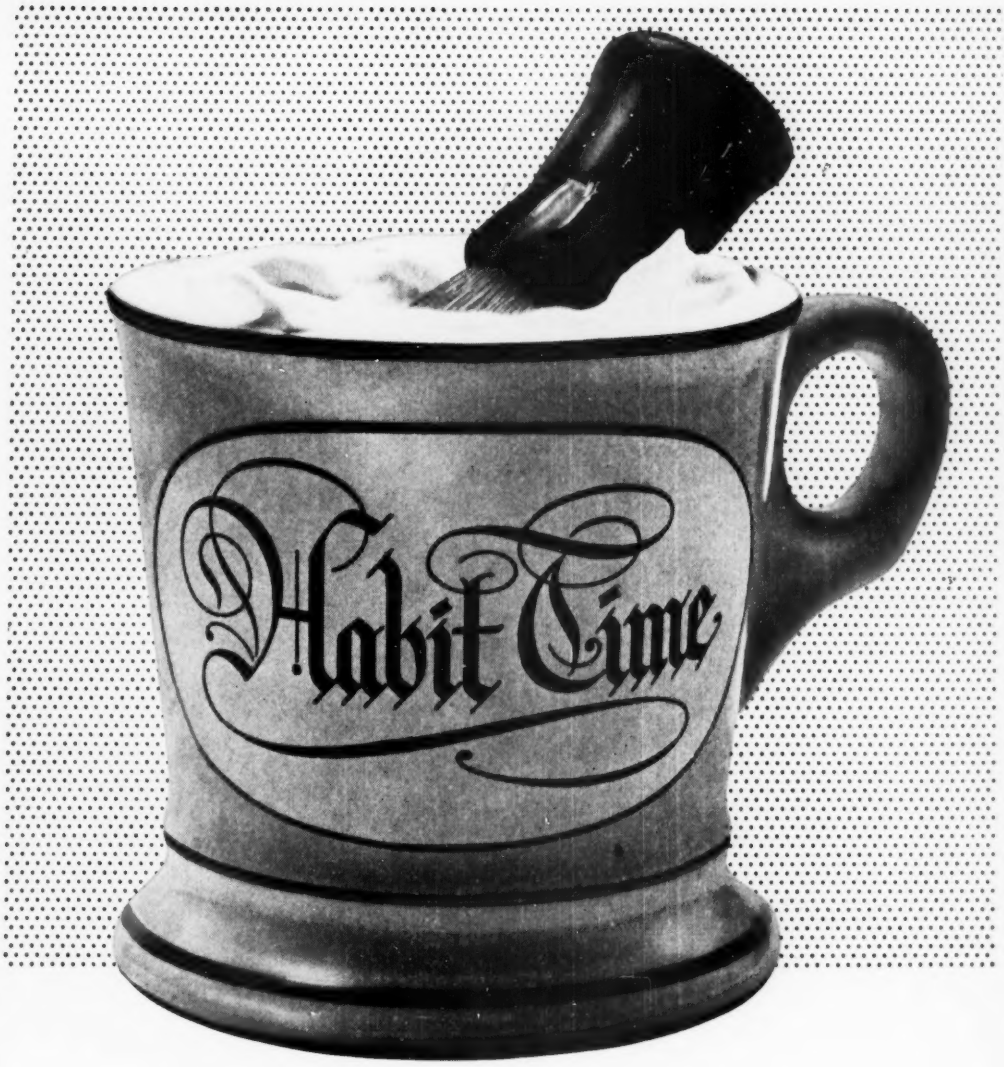

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